SCLC – Treatment & advances

Dr Gunda Jaya Hareesh

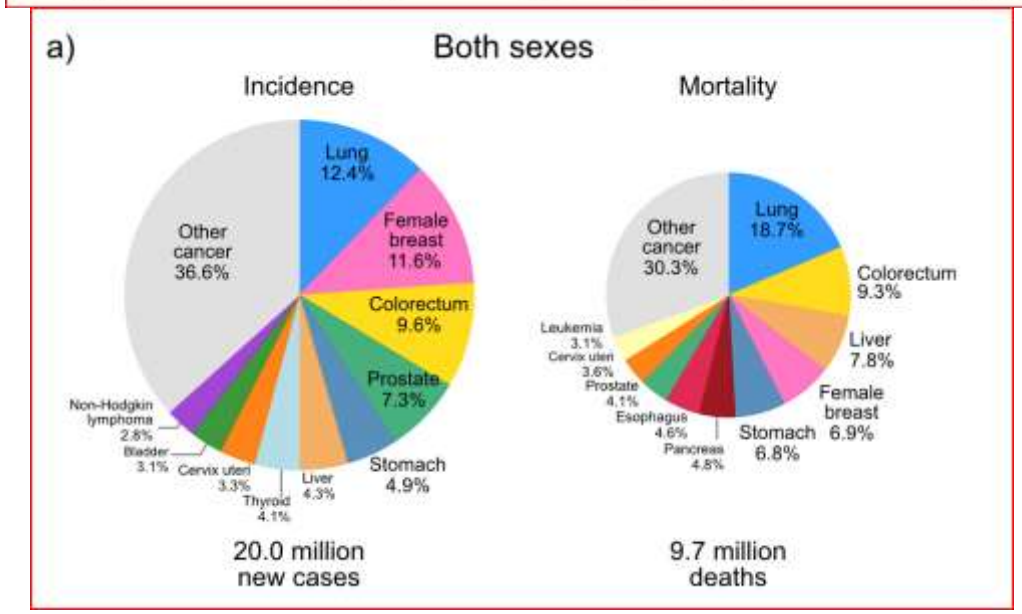
EPIDEMIOLOGY

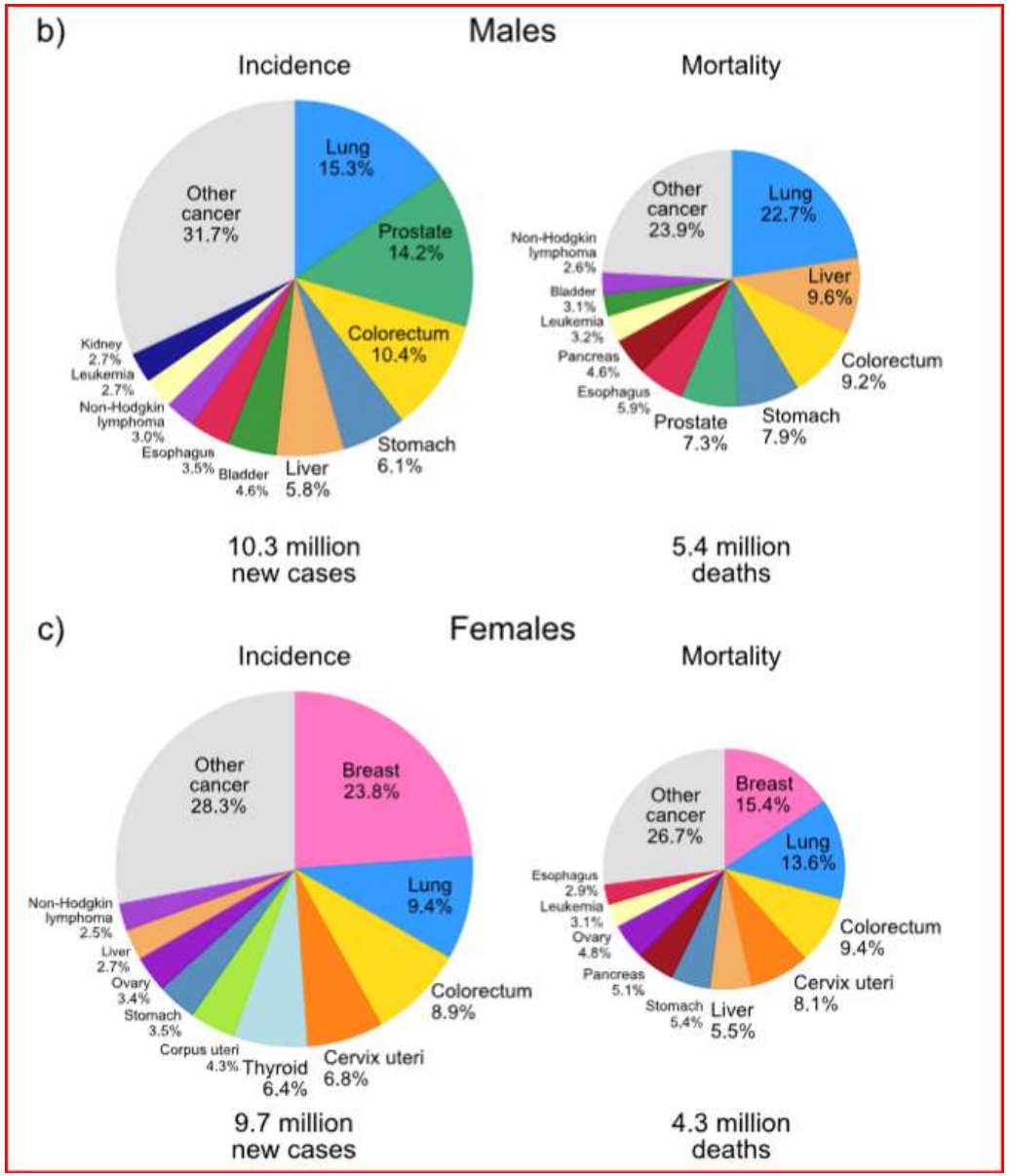
Estimated New Cases

Male			Female		
Prostate	299,010	29%	Breast	310,720	32%
Lung & bronchus	116,310	11%	Lung & bronchus	118,270	12%
Colon & rectum	81,540	8%	Colon & rectum	71,270	7%
Urinary bladder	63,070	6%	Uterine corpus	67,880	7%
Melanoma of the skin	59,170	6%	Melanoma of the skin	41,470	4%
Kidney & renal pelvis	52,380	5%	Non-Hodgkin lymphoma	36,030	4%
Non-Hodgkin lymphoma	44,590	4%	Pancreas	31,910	3%
Oral cavity & pharynx	41,510	4%	Thyroid	31,520	3%
Leukemia	36,450	4%	Kidney & renal pelvis	29,230	3%
Pancreas	34,530	3%	Leukemia	26,320	3%
All sites	**1,029,080**		**All sites**	**972,060**	

Estimated Deaths

Male			Female		
Lung & bronchus	65,790	20%	Lung & bronchus	59,280	21%
Prostate	35,250	11%	Breast	42,250	15%
Colon & rectum	28,700	9%	Pancreas	24,480	8%
Pancreas	27,270	8%	Colon & rectum	24,310	8%
Liver & intrahepatic bile duct	19,120	6%	Uterine corpus	13,250	5%
Leukemia	13,640	4%	Ovary	12,740	4%
Esophagus	12,880	4%	Liver & intrahepatic bile duct	10,720	4%
Urinary bladder	12,290	4%	Leukemia	10,030	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	10,690	3%	Brain & other nervous system	8,070	3%
All sites	**322,800**		**All sites**	**288,920**	





Siegel RL, et al Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12–49
Bray F et al. CA Cancer J Clin. 2024 May-Jun;74(3):229-263

- Neuroendocrine tumors accounts for 20% lung cancers – of which 14% are SCLC
- SEER database [2] - SCLC incidence - 8.8/100,000 in 2000 to 4.8/100,000 in 2019 (45.5% decline)

  Male-to-female ratio - 1.14:1 in 2000 to 0.93:1 in 2019

  SCLC relative to NSCLC declined from 14.5% in 2000 to 11.8% in 2019.

  LS SCLC cases decreased from 31.1% in 2000 to 26.4% in 2019
  - 2-year OS increased from 26.7% (2000) to 36.7% (2017).
  - 5-year OS increased from 11.3% (2000) to 15.6% (2014).
  - ES-SCLC:
    - 2-year OS increased from 6.4% (2000) to 8.4% (2017).
    - 5-year OS increased in females (2.2% to 3.9%) but remained stable in males (2.3% to 2.0%).

Siegel RL, et al Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12–49
Cohen, Sean et al. Journal of Clinical Oncology (2023)

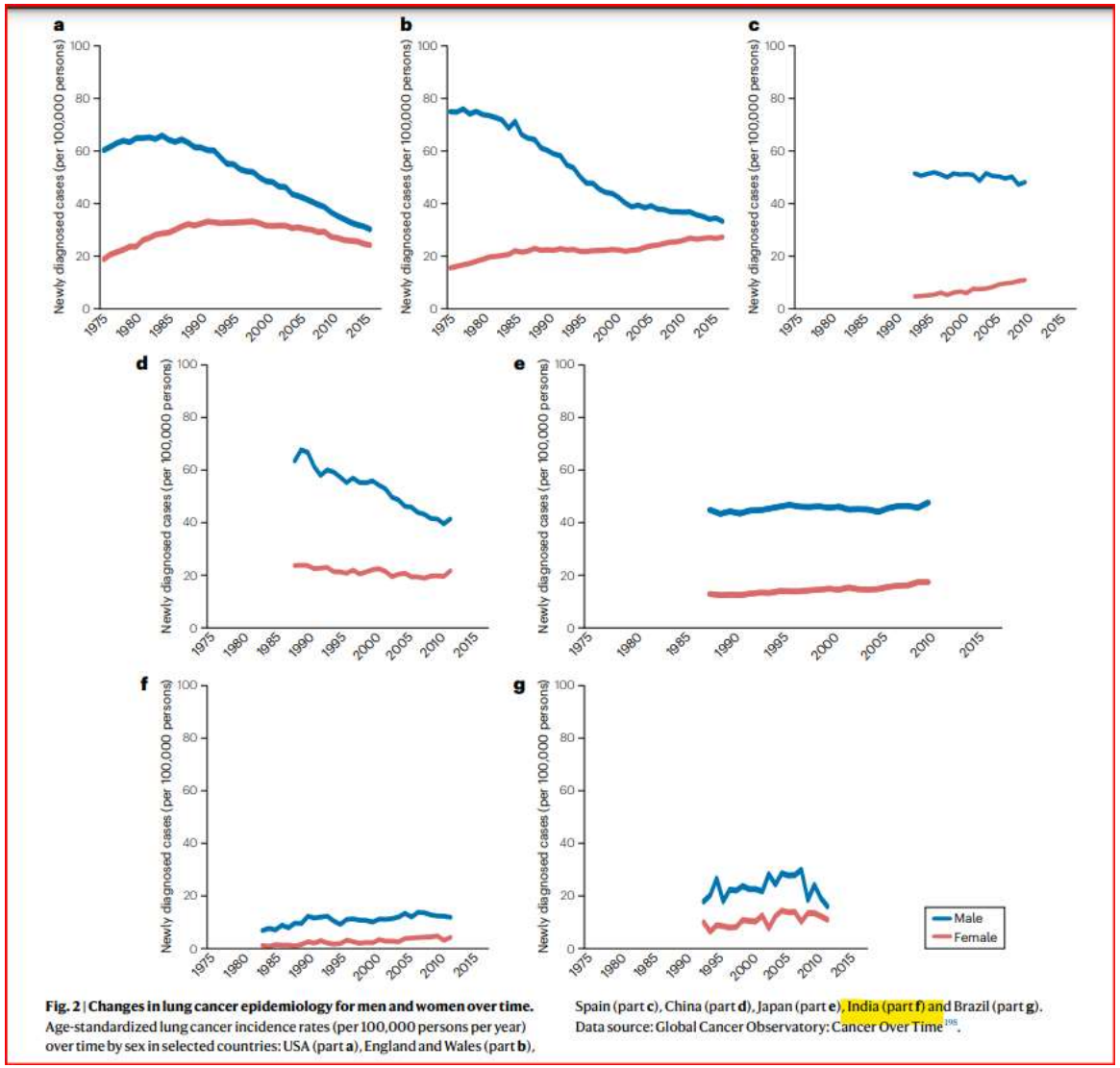
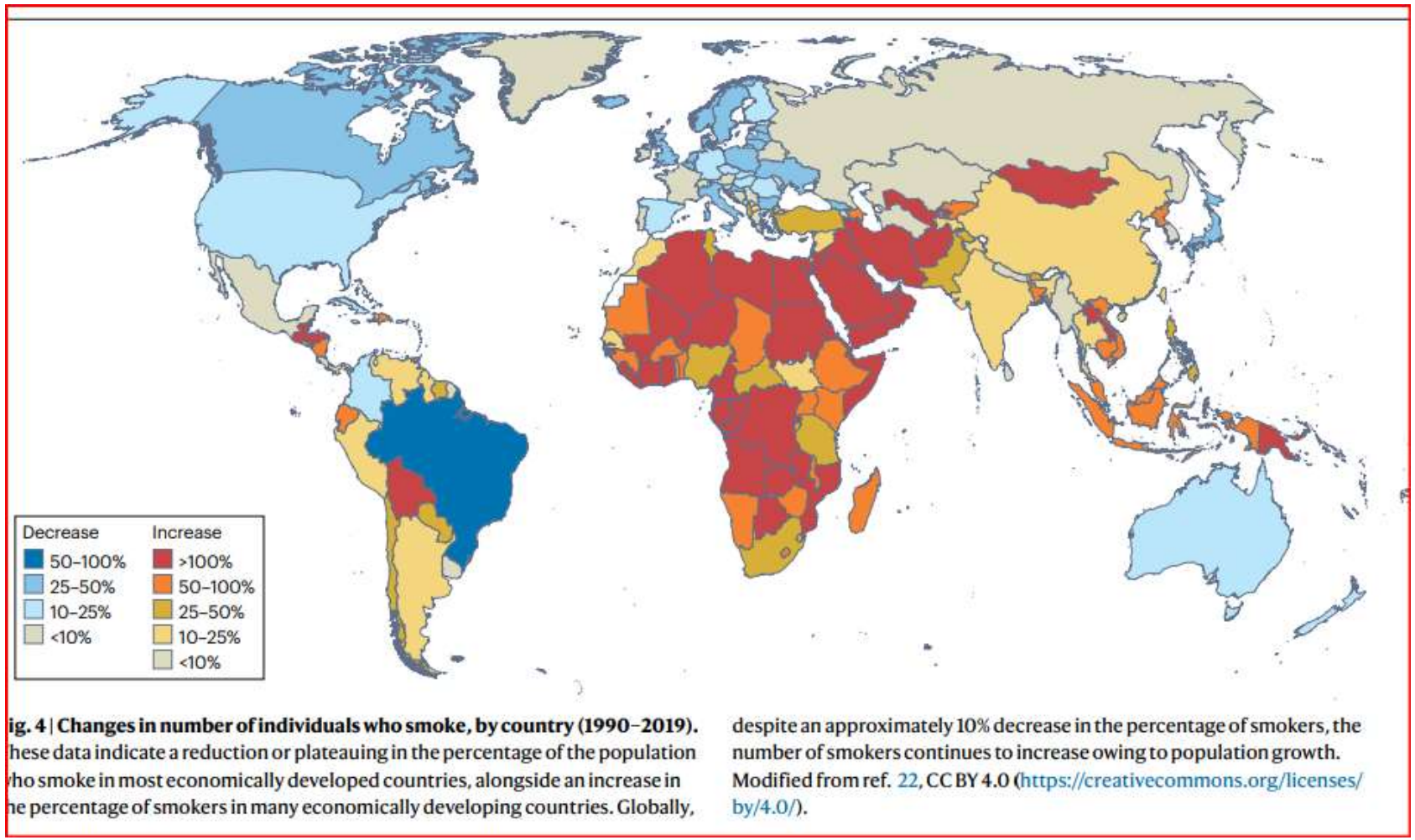


Fig. 2 | Changes in lung cancer epidemiology for men and women over time. Age-standardized lung cancer incidence rates (per 100,000 persons per year) over time by sex in selected countries: USA (part **a**), England and Wales (part **b**), Spain (part **c**), China (part **d**), Japan (part **e**), India (part **f**) and Brazil (part **g**). Data source: Global Cancer Observatory: Cancer Over Time[195].

Leiter, A. et al, Nat Rev Clin Oncol 20, 624–639 (2023)



ig. 4 | Changes in number of individuals who smoke, by country (1990–2019). hese data indicate a reduction or plateauing in the percentage of the population who smoke in most economically developed countries, alongside an increase in he percentage of smokers in many economically developing countries. Globally, despite an approximately 10% decrease in the percentage of smokers, the number of smokers continues to increase owing to population growth. Modified from ref. 22, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

28 population-based cancer registries and 58 hospital-based cancer registries across a five-year (2012-2016)

Table II. Age distribution and histologic type of lung cancer according to IC0-0-3 classification

Age group (yr)	Epithelial tumours-adenocarcinoma, n (%)	Epithelial tumours-squamous cell carcinoma, n (%)	Small cell carcinoma, n (%)	Non-small cell carcinoma, n (%)	Epithelial tumours-others, n (%)	Lymph histiocytic tumours, n (%)	Mesenchymal tumours, n (%)	Others*, n (%)	Total number of lung cancers, n (%)
				Males					
0-14	5 (0.1)	1 (0)	0	0	0	1 (3.6)	6 (13.0)	2 (0)	15 (0.1)
15-24	32 (0.5)	8 (0.2)	2 (0.1)	2 (0)	1 (0)	4 (14.3)	3 (6.5)	3 (0.2)	55 (0.3)
25-34	152 (2.5)	22 (0.5)	14 (0.8)	37 (1)	18 (2)	4 (14.3)	5 (10.9)	31 (1.7)	283 (1.6)
35-44	412 (6.9)	124 (3.0)	71 (4.0)	144 (5.3)	65 (7)	3 (10.7)	2 (4.3)	118 (6.5)	939 (5.4)
45-54	1293 (21.6)	613 (15.0)	364 (20.7)	512 (18.8)	186 (19)	4 (14.3)	7 (15.2)	436 (24.2)	3415 (19.6)
55-64	2098 (35.1)	1547 (37.9)	701 (39.9)	988 (36.2)	361 (37)	6 (21.4)	13 (28.3)	637 (35.3)	6351 (36.5)
65-74	1548 (25.9)	1319 (32.3)	486 (27.7)	792 (29.0)	259 (27)	4 (14.3)	9 (19.6)	454 (25.2)	4871 (28.0)
75+	439 (7.3)	449 (11.0)	117 (6.7)	252 (9.2)	79 (8)	2 (7.1)	1 (2.2)	121 (6.7)	1460 (8.4)
Total	5979 (100)	4083 (100)	1755 (100)	2727 (100)	970 (100)	28 (100)	46 (100)	1803 (100)	17,391 (100)
				Females					
0-14	1 (0.0)	0	0	1 (0.2)	1 (0.3)	0	1 (4.5)	0	4 (0.1)
15-24	14 (0.5)	3 (0.5)	7 (2.2)	4 (0.6)	3 (0.9)	0	1 (4.5)	1 (0.2)	33 (0.6)
25-34	117 (4.2)	12 (2.0)	11 (3.5)	21 (3.4)	13 (4.0)	0	5 (22.7)	19 (3.3)	198 (3.8)
35-44	363 (13.1)	53 (8.8)	37 (11.7)	56 (9.0)	38 (11.6)	2 (11.8)	3 (13.6)	82 (14.3)	634 (12.1)
45-54	715 (25.8)	123 (20.4)	72 (22.7)	143 (23.1)	93 (28.3)	4 (23.5)	6 (27.3)	143 (25.0)	1299 (24.7)
55-64	877 (31.6)	192 (31.8)	107 (33.8)	204 (33.0)	88 (26.7)	8 (47.1)	5 (22.7)	185 (32.3)	1666 (31.7)
64-74	525 (18.9)	182 (13.1)	63 (19.9)	143 (23.1)	71 (21.6)	3 (17.6)	1 (4.5)	115 (20.1)	1103 (21.0)
75+	161 (5.8)	39 (6.5)	20 (6.3)	47 (7.6)	22 (6.7)	0	0	28 (4.9)	317 (6.0)
Total	2773 (100)	604 (100)	317 (100)	619 (100)	329 (100)	17 (100)	22 (100)	573 (100)	5254 (100)

*Others, bronchioalveolar; large cell; adenosquamous; mesothelioma; carcinoma NOS. NOS, not otherwise specified

- Male:Female ::5.5:1
- Male – 10.1%
- Female – 6%
- Total – 9.1%

Nath A et al Indian J Med Res. 2022 Feb;155(2):264-272

History

- In 1926 - Barnard described SCLC histology as “oat cell sarcoma of mediastinum” – he recognized its bronchial origin – proposed renaming it to bronchial carcinoma (as it arose from germinal cells found in the basal layer of bronchial epithelium)
- 1959 – Azzopardi provided a histochemical description of 100 cases of oat cell carcinoma
- 1962 – Watson and Berg et al. analyzed 3600 lung cancer cases in the Thoracic Service Registry of the Memorial Hospital for Cancer and Allied Diseases, New York – 386 cases as identified (initially classified as anaplastic carcinoma) – described clinical features, radiology, and treatment

Barnard WG. 1926. J Pathol Bacteriol 29: 241–244
Watson WL, Berg JW Cancer. 1962 Jul-Aug;15:759-68

TABLE I

FREQUENCY OF OAT CELL CARCINOMAS IN ENTIRE SERIES AND IN PATIENTS WITH RESECTABLE TUMORS

Type carcinoma	% tot. series	% resect. tum.
Oat cell	11	7
Squamous	40	60
Adenocarcinoma	11	15
Terminal bronchiolar	5	10
Large cell anaplastic	33	8

- Origin – from reserve cells beneath the columnar layer
- Primarily men and smokers - 353 men vs 33 women (11:1) & 8:1
- 30 yrs – 83 yrs (72% between 50-70 yrs)
- 62% heavy smokers 9% minimal use and 2.8% never smoked
- 1.3% discovered by chance and shorter duration of symptoms
- Cough (50% productive), chest pain, swelling of face and neck
- Hemoptysis – 4.4%

Treatment –

- 90% of cases showed a favorable clinical response and 50% showed radiographic regression
- Response to nitrogen mustard is predicable, a kind of physiological diagnostic test for oat cell carcinoma
- 30 patients treated – 28 died within a year (a good response)

  Only 2 survived for more than a year

Watson WL, Berg JW Cancer. 1962 Jul-Aug;15:759-68

TABLE 2

TYPES OF RESECTION PERFORMED IN THE 27 (7%) OAT CELL TUMORS FOUND TO BE RESECTABLE

Operation		No. pt.
Pneumonectomy		18
Radical	9	
Simple	9	
Lobectomy		6
Radical	2	
Simple	4	
Wedge resection		3
Simple	2	
Simple+Ir^{192} & P^{32}*	1	

*The patient received radioactive iridium and radioactive phosphorus.

TABLE 3

SURVIVAL OF PATIENTS WITH OAT CELL CARCINOMA AFTER RESECTION

Survival, yr.	No. pt.
<1	14
1-2	4
2-3	5*
3-4	1
4-5	1
5-6	1*
6-12	...
12-13	1*

*One patient alive and well in each time category.

TABLE 5

SURVIVAL OF PATIENTS WITH OAT CELL CARCINOMA TREATED PRIMARILY BY METHODS OTHER THAN OPERATION

Treatment	No. pt.	Survival, yr. <1	1-2	2-3	7+
Radiation only	80	72	7	1	...
Radiation & radioisotopes	2	2	...	...	...
Chemotherapy only	30	28	2	...	...
Chemotherapy & radiation	95	82	6	6	1*

*The patient is alive and well.

TABLE 7

SITE OF METASTASES FOUND IN 76 PATIENTS WITH OAT CELL CARCINOMA AT AUTOPSY

Site	Metastases No. pt.	% pt.
Lymph nodes (reg. & dist.)	67	88
Liver	44	58
Adrenals*	39	51
Bone	34	45
Pancreas	31	40
Opposite lung	26	34
Kidney†	21	28
Thyroid	17	22
Brain‡	14	37

*In 9 instances, 1 adrenal was involved; in 30, both were involved.

†In 10 instances, 1 kidney was involved; in 11, both were involved.

‡In 38 instances, the brain was examined at autopsy. There was metastatic disease in 14 and no metastatic disease in 24 instances.

TABLE 6

LOCATION OF PRIMARY TUMOR FOUND AT AUTOPSY IN 70 CASES OF OAT CELL LUNG CANCER

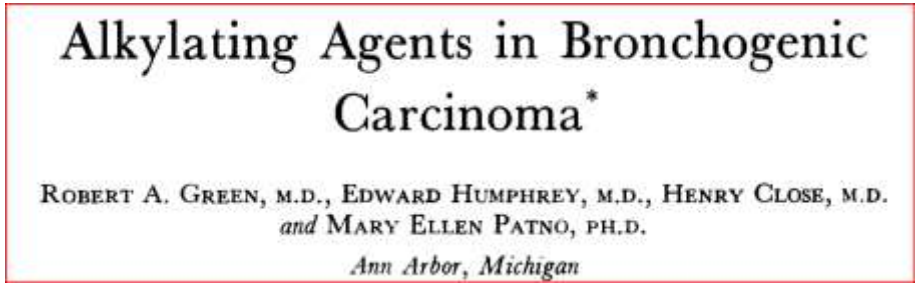
Site primary	No. pt.		% pt.	
Right lung		41		58
Upp. lobe	37		53	
Mid. lobe	1		1	
Low. lobe	3		4	
Left lung		29		42
Upp. lobe	25		36	
Low. lobe	4		6	

Watson WL, Berg JW Cancer. 1962 Jul-Aug;15:759-68

- 1965 – 1968 – Bensch et al. described electron-opaque granules in tumor cells and later identified a similar cell type in normal bronchial epithelium resembling argentaffin (Kultschitzky) cells in the GIT suggesting a neuroendocrine (NE) origin
- 1968 - Veterans Administration Lung Cancer Study Group

  Divided bronchogenic carcinoma into 2 types

  - Limited stage - apparently localized to one hemithorax, although scalene lymph nodes positive for metastatic tumor could be included if the nodes had not been palpated clinically.
  - Extensive stage -
- 7 protocols of chemotherapy were studied vs an inert drug (3 for nitrogen mustard and 4 protocols of cyclophosphamide)



Alkylating Agents in Bronchogenic Carcinoma*

ROBERT A. GREEN, M.D., EDWARD HUMPHREY, M.D., HENRY CLOSE, M.D. and MARY ELLEN PATNO, PH.D.

Ann Arbor, Michigan

Barnard WG. 1926. J Pathol Bacteriol 29: 241–244
Green RA et al. Am J Med. 1969 Apr;46(4):516-25

TABLE I

HISTOLOGIC CLASSIFICATION OF CARCINOMA OF LUNG

Cell Group	Classification
Squamous cell carcinomas	1
Highly differentiated	1a
Moderately differentiated	1b
Slightly differentiated	1c
Small cell carcinomas	2
Oval cell structure (oat cell)	2a
Polygonal cell structure	2b
Adenocarcinomas	3
Acinar	3a
Papillary	3b
Chiefly "large cells"	3c
Large cell undifferentiated carcinomas	4
Combined epidermoid and adenocarcinomas	5

TABLE II

PER CENT SURVIVAL TO INDICATED MONTH

Inert Compound, All Cases, Protocols 1–6 Versus Nitrogen Mustard (HN_2), All Cases, Protocols 1–3

	Per Cent Survival									
	All Cases		1a & 1b		1c & 4		2a & 2b		3a, 3b & 3c	
Month	Inert	HN_2	Inert	HN_2	Inert	HN_2	Inert	HN_2	Inert	HN_2
2	74	79	80	83	73	76	68	77	74	79
3	57	63	66	73	51	62	44	59	66	47
4	45	51	51	68	43	47	33	43	46	36
5	37	38	40	54	36	34	24	29	41	31
7	24	30	29	50	23	25	14	21	27	19
10	13	17	14	29	12	14	7	5	16	13
13	9	13	10	22	8	13	3	2	7	8
No. treated	946	293	229	66	300	91	127	70	136	38
$X^2(2)$	3.3		10.6		3.0		3.5		0.3	
Approximate p	0.20		0.005		0.22		0.18		0.86	

TABLE V

PER CENT SURVIVAL TO INDICATED MONTH

Inert Compound (Extensive Disease), Protocols 2–6 Versus Intravenous Cyclophosphamide (Cyclo), (Extensive Disease), Protocols 4–6

	All Cases		1a & 1b		1c & 4		2a & 2b		3a, 3b, 3c	
Month	Inert	Cyclo	Inert	Cyclo	Inert	Cyclo	Inert	Cyclo	Inert	Cyclo
2	68	74	76	69	69	75	60	88	68	71
3	50	58	61	58	43	55	37	70	57	57
4	38	47	43	46	37	45	25	58	46	43
5	30	38	32	40	31	38	17	49	39	31
7	19	24	23	28	17	22	10	29	24	15
10	11	11	14	15	11	9	6	9	13	8
13	7	7	8	11	8	6	2	6	6	5
No. treated	616	426	124	81	204	139	87	57	101	69
$X^2(2)$	7.53		0.97		4.71		15.2		1.18	
Approximate p	0.02		0.61		0.10		0.0005		0.55	

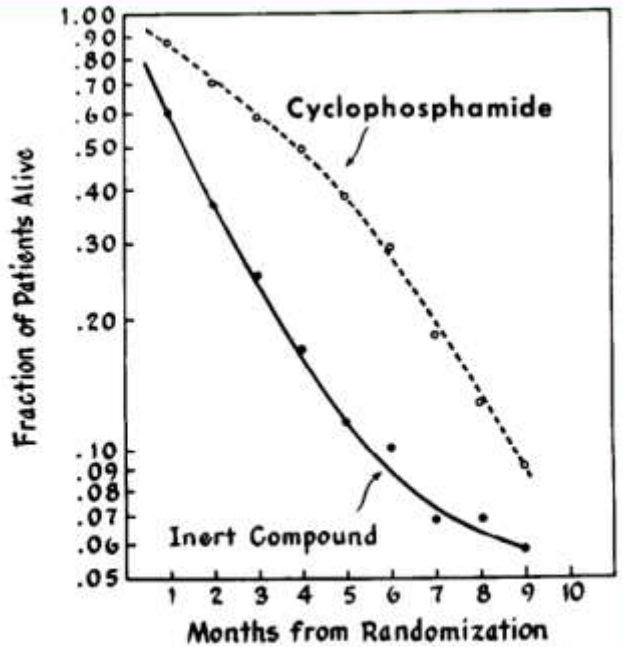


FIG. 2. Undifferentiated small cell carcinoma. Cyclophosphamide versus inert compound.

FIVE-YEAR FOLLOW-UP OF THE MEDICAL RESEARCH COUNCIL COMPARATIVE TRIAL OF SURGERY AND RADIOTHERAPY FOR THE PRIMARY TREATMENT OF SMALL-CELLED OR OAT-CELLED CARCINOMA OF THE BRONCHUS

A REPORT TO THE MEDICAL RESEARCH COUNCIL WORKING PARTY* ON THE EVALUATION OF DIFFERENT METHODS OF THERAPY IN CARCINOMA OF THE BRONCHUS

A. B. MILLER WALLACE FOX

- 1969 – 29 thoracic surgical centers – Britain

  Small cell carcinoma on histology with no extrathoracic metastasis regarded operable, fit for resection and radical radiotherapy
- 144 patients – 71 to surgery and 73 to radical-radiotherapy
- Surgery arm – 48% complete resection and 18% no surgery
- Radiotherapy arm – 85% radical, 11% palliative and 4% no radiotherapy

TABLE II—SURVIVAL IN THE TWO SERIES

Series	Group	Total	Patients alive at (month): 3		6		12		18		24		36		48		60		Mean survival (days)	
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Surgery (S) ..	All patients	71	57	80	32	45	15	21	5	7	3	4	2	3	2	3	1	1	199	
Radical radiotherapy (R)	All patients	73	65	89	45	62	16	22	9	12	7	10	5	7	5	7	3	4	284	
Surgery (S) ..	Complete resection	34	31	91	18	53	8	24	3	9	2	6	1	3	1	3	0	0	240	199
	Thoracotomy only	24	16	(67)	9	(38)	4	(17)	1	(4)	0	(0)	0	(0)	0	(0)	0	(0)	148	
	No surgery	13	10	(77)	5	(38)	3	(23)	1	(8)	1	(8)	1	(8)	1	(8)	1	(8)	199	
Radical radiotherapy (R)	Radical	62	56	90	40	65	16	26	9	15	7	11	5	8	5	8	3	5	312	293
	Palliative	8	7	(88)	5	(62)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	169	
	No radiotherapy	3	2	(67)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	112	

Parentheses indicate percentages based on less than 25 observations.

TABLE I—TREATMENT PATIENTS RECEIVED DURING THE 5-YEAR PERIOD

Series	Initial treatment	Total patients	Patients who had treatment in addition to that allocated									
			All patients having additional treatment		Surgery		Radiotherapy				Cytotoxic chemotherapy	
							For primary growth or mediastinal spread		For distant metastases			
			No.	%	No.	%	No.	%	No.	%	No.	%
Surgery (S)	Complete resection	34	20	59	5	15	8	24	5	15	8	24
	Thoracotomy only*	24	14	(58)	1	(4)	11	(46)	2	(8)	3	(12)
	No surgery	13	10	(77)	0	(0)	9	(69)	1	(8)	3	(23)
	All patients	71	44	62	6	8	28	39	8	11	14	20
Radical radiotherapy (R)	Radical radiotherapy	62	18	29	1	2	3	5	12	19	5	8
	Palliative radiotherapy	8	3	(38)	0	(0)	0	(0)	1	(12)	3	(38)
	No radiotherapy	3	1	(33)	1	(33)	0	(0)	0	(0)	1	(33)
	All patients	73	22	30	2	3	3	4	13	18	9	12

* Including 1 patient who had an incomplete resection.
Parentheses indicate percentages based on less than 25 observations.

Mean survival 199 vs 284 days ($p<0.05$)

	At 2 yr	At 4 yrs	At 5 yrs
Surgery	4%	3%	1%
Radiotherapy	10%	7%	4%

- 1994 -

All received chest and brain irradiation concurrently
50 Gy in 25# to chest
30 Gy in 15# to the whole brain

82% had >90% KFS
5% had residual ds > 5 cm

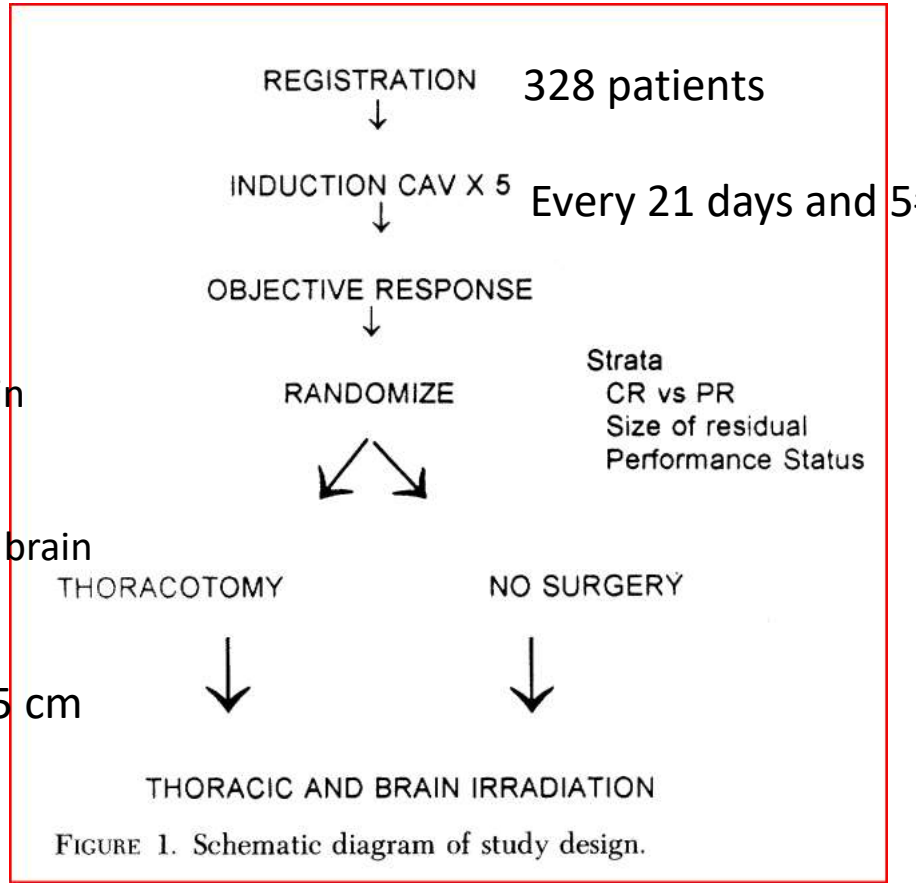


FIGURE 1. Schematic diagram of study design.

A Prospective Randomized Trial to Determine the Benefit of Surgical Resection of Residual Disease Following Response of Small Cell Lung Cancer to Combination Chemotherapy*

Thomas Lad, MD; Steven Piantadosi, MD, PhD; Paul Thomas, MD, FCCP; David Payne, MD; John Ruckdeschel, MD, FCCP; and Giuseppe Giaccone, MD

Table 1—*Study Census*

	No.	(%)	No.	(%)
Patients registered			328	
Responders			217	(66)
Complete	90	(27)		
Partial	127	(39)		
Nonresponders			111	(34)
Died during induction	10			
Progressed during induction	45			
Inadequate shrinkage	56			
Eligible for randomization			217	
Randomized			146	(44)
Surgery	70			
No surgery	76			
Not randomized			71	

Table 2—*Responders Not Randomized*

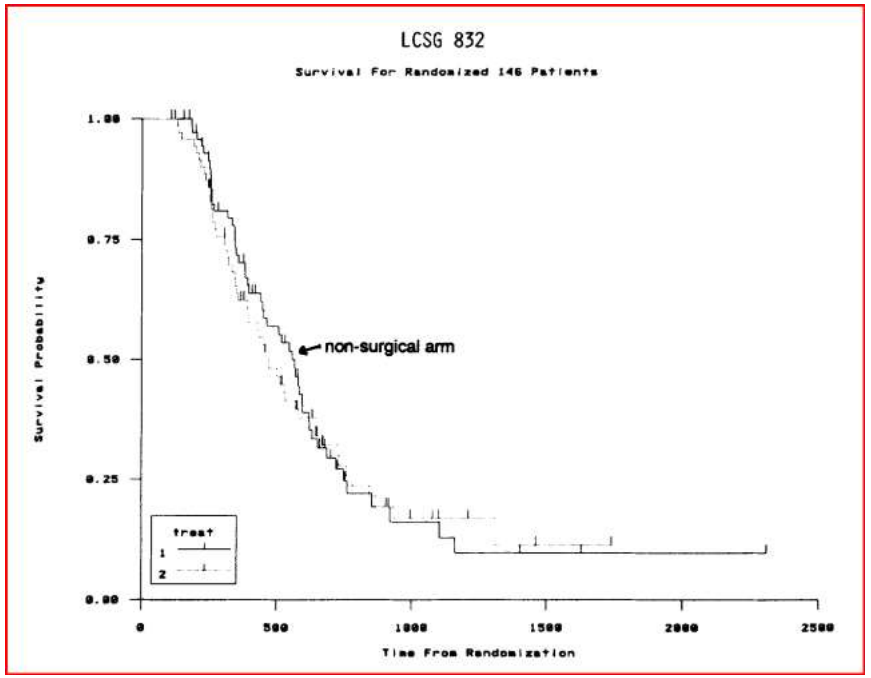
	No.
Refused randomization	32
Requested surgery	8
Protocol violation	6
Medically inoperable	14
Judged unresectable	12
Metastatic disease	4
Died prior to randomization	2
Second primary (larynx)	1

Table 3—*Thoracotomy Results*

	No.		(%)
Randomized to surgical treatment	70		
Refused surgery	8		
	62		
Off-study surgery	8		
Total No. of thoracotomies	70		
Resection	58		(83)
Complete		54	
Incomplete (positive margins)		4	
Unresectable (open and close)	12		(17)
Postoperative death	2		(3)

Table 4—*Pathology Findings: Analysis of Thoracotomy Specimens*

	No.		(%)
No. of cases	70		
Residual small cell cancer	51		(73)
No residual small cell cancer	19		(27)
No tumor in specimen	13		(19)
Non-small cell histologic features	8		(11)
Adenocarcinoma		2	
Large cell carcinoma		1	
Atypical carcinoid		3	
Small cell+squamous		1	
Small cell+large cell		1	



Median survival	
Surgical arm	15.4 months
Non surgical arm	18.4 months

The role of surgery in stage I to III small cell lung cancer: A systematic review and meta-analysis

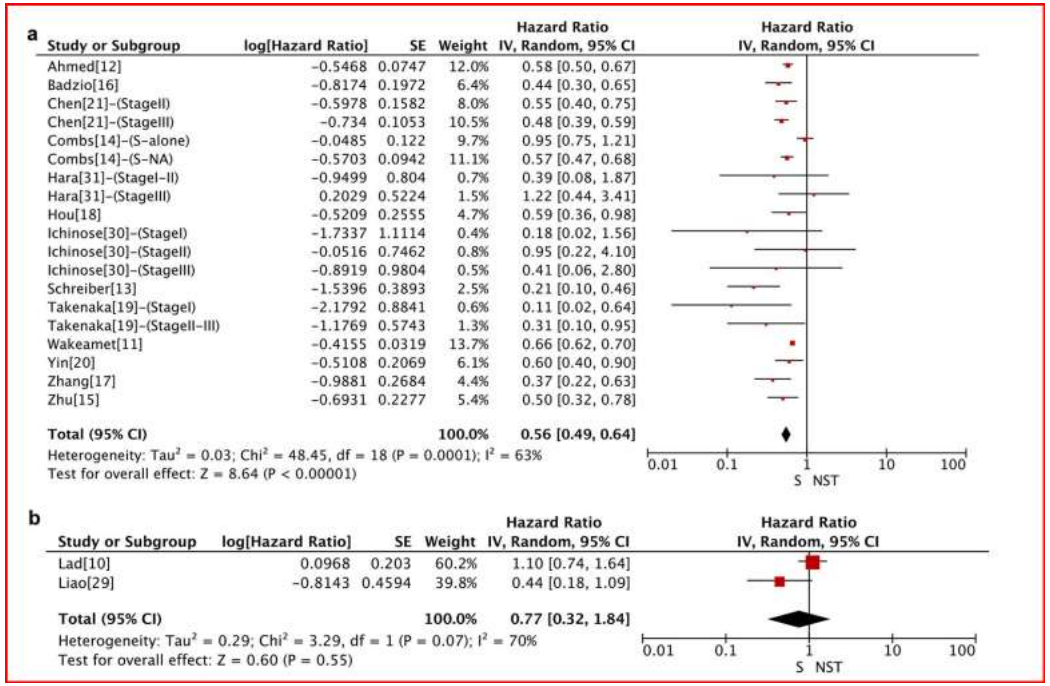
Tingting Liu, Zihao Chen, Jun Dang*, Guang Li

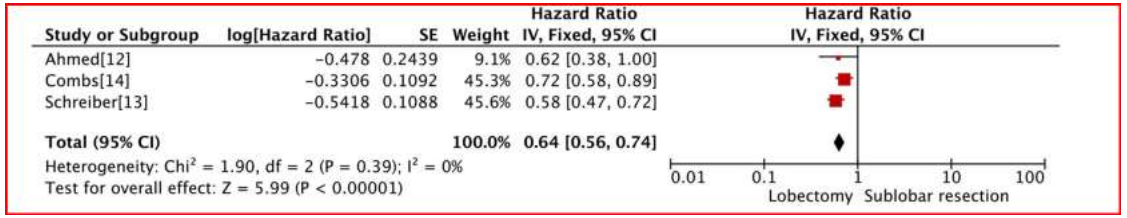
- 2 RCTs and 13 retrospective studies = 41,483 patients
- Stage I-III SCLC diagnosed by cytology and histopathology

Table 2. Subgroup and meta-regression analysis of the effect on OS from surgical treatment.

Subgroup	Included studies No. [References]	No. of Patients (Surgery/NST)	HR [95% CI]	Heterogeneity		Meta-regression
				I^2 (%)	P-Value	P-Value
Sample size						0.61
≥ 100	12 [11–18,20–21]	4719/36290	0.56 [0.49–0.64]	72	< 0.001	
< 100	7 [19,30–31]	161/127	0.49 [0.28–0.83]	27	0.22	
Publication date						0.58
Before 2004	5 [30–31]	73/77	0.70 [0.36–1.35]	0	0.45	
After 2004	14 [11–21]	4807/36340	0.55 [0.48–0.63]	71	< 0.001	
Surgical treatment type						0.01
Surgery + NST	15 [11–12,14–18,20,30–31]	3299/19403	0.60 [0.53–0.67]	39	0.06	
Surgery alone	5 [11–12,14]	857/18950	0.87 [0.71–1.06]	70	0.01	
Clinical stage						0.16
Stage I	6 [11–12,14,16,19,30]	2429/4746	0.56 [0.49–0.64]	54	0.05	
Stage II	8 [11,14–16,19–20–21,30]	613/3550	0.75 [0.57–0.99]	64	0.006	
Stage III	10 [11,13–14,16–17,19–21,30–31]	917/22542	0.70 [0.56–0.88]	74	< 0.001	

Abbreviations: NST: non-surgical treatment.





Conclusions

Surgery-based multi-modality treatment appears to be associated with a favorable survival advantage in stage I and selected stage II to III SCLC. Lobectomy is likely to provide superior OS when compared to sublobar resection. Further prospective RCTs are needed to confirm these findings.

Liu T, Chen Z, Dang J, Li G (2018) PLoS ONE 13(12): e0210001.

CURRENT PRINCIPLES OF SURGICAL RESECTION

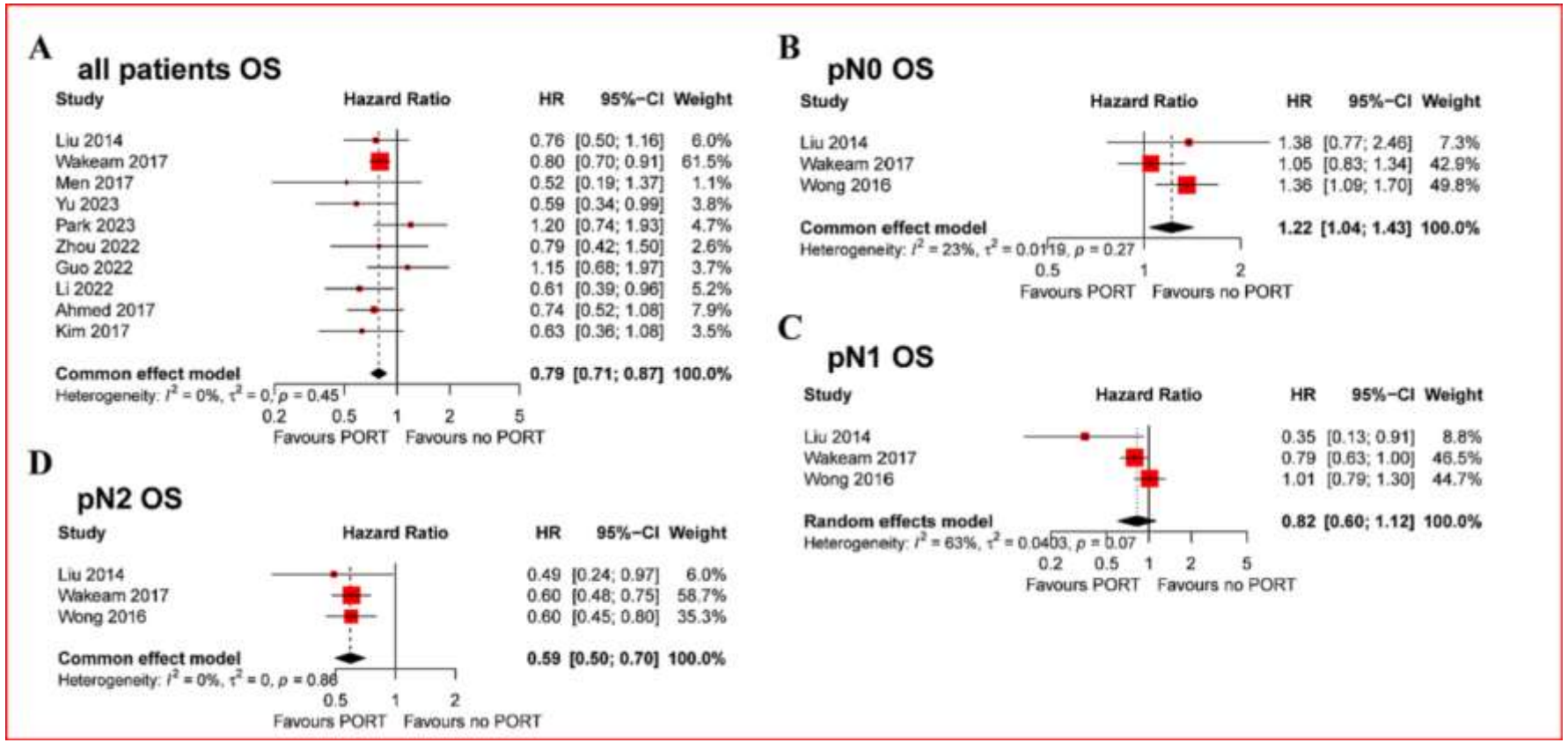
- Clinical stage I–IIA (T1–2, N0, M0) SCLC, selected patients of T3 N0
- Before resection, mediastinoscopy or other surgical mediastinal staging (e.g., endoscopic staging) is necessary to rule out occult nodal disease
- For definitive surgical resection, lobectomy with mediastinal lymph node dissection or systematic lymph node sampling (≥3 N2 and ≥1 N1 stations) is preferred
- Patients with complete resection should receive postoperative systemic therapy
- Nodal metastases (N2/N3) require concurrent or sequential systemic therapy and mediastinal RT, while N1 may consider postoperative mediastinal radiation
- The benefit of PCI is unclear for patients with definitive therapy for pathologic stage I (T1-2a, N0, M0)

Original Article

Application of postoperative adjuvant radiotherapy in limited-stage small cell lung cancer: A systematic review and meta-analysis

Chuanhao Zhang [a,b,1], Genghao Zhao [b,1], Huajian Wu [b,c], Jianing Jiang [b], Wenyue Duan [b], Zhijun Fan [b], Zhe Wang [b,c,*], Ruoyu Wang [b,c,*]

- 11 retrospective studies = 7694 eligible participants of LS-SCLC



- Post operative radiotherapy – pN2 and pN1 +/-
- Can be sequential or concurrent with chemotherapy

Zhang C et al Radiother Oncol. 2024 Apr;193:110123

Stage I-IIA who are not surgically fit?

- Retrospective study of 43 stage I SCLC patients who have undergone stereotactic body radiotherapy (SBRT) -- 2 yr OS, PFS, DMFS was 72.3%, 44.6%, 47.2% respectively with 2 yr local control being 80.2% and no grade > 3 toxicities (chemotherapy and PCI was given among 8 patients alone) [1]
- A prospective study from 24 centers among 74 patients with stage I SCLC showed that the addition of chemotherapy showed significant benefit to SBRT alone (chemotherapy in 56% and PCI in 23% cases)[2]

  1-yr and 3-yr local control rate - 97.4% and 96.1%

  1-yr and 3-yr OS - 69.9%, and 34.0%

  chemotherapy vs no chemotherapy – OS ----31.4 vs 14.3 months (p=0.02)

  DFS ---- 61.3 vs 9 months (p=0.02)

1. Shioyama Y et al. Technol Cancer Res Treat. 2018 Jan 1;17:1533033818783904
2. Verma V et al. Clin Lung Cancer 2017 Nov;18(6):675-681.e1

Radiotherapy

- Meta analysis by Pigeon et al in 1992 showed chemoradiotherapy is superior over chemotherapy alone – which showed a 14% reduction in mortality rate more pronounced in age < 55 (28% reduction) and OS benefit at 3 yrs was 5.4% [1]

Concurrent vs sequential ????

- Takada et al. in 2002 – 231 patients with LS-SCLC randomized to sequential (4# of cisplatin + etoposide Q3W followed by Radiotherapy – 45Gy over 3 weeks) vs concurrent RT (4# of cisplatin + etoposide Q4W and RT should begun on day 2 of first cycle)

Pignon JP et al. N Engl J Med. 1992 Dec 3;327(23):1618-24

Concurrent vs sequential RT?

Table 1. Characteristics of Patients According to Treatment Arm: Eligible Patients

Characteristic	Sequential Arm (n = 114)* No. of Patients	%	Concurrent Arm (n = 114) No. of Patients	%	P
Age, years					
Median	64		65		.46
Range	30-74		39-74		
Sex					
Male	93	82	91	80	.87
Female	21	18	23	20	
PS					
0	33	29	25	22	.49
1	75	66	83	73	
2	6	5	6	5	
Weight loss					
< 10%	102	89	104	91	.86
≥ 10%	8	7	6	5	
Not reported	4	4	4	4	
Stage					
II	10	9	7	6	.54
IIIA	57	50	65	57	
IIIB	47	41	42	37	

*Three patients in the sequential arm were ineligible because of being in the extensive stage in two patients and having lymphoma in one patient. They were excluded from Table 1.

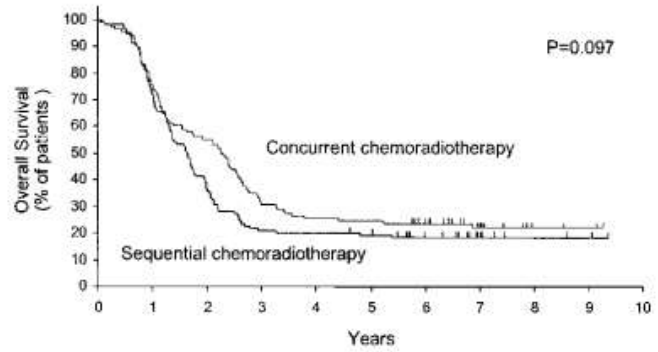


Fig 1. Overall survival of patients with LS-SCLC who were assigned to treatment with sequential chemoradiotherapy or concurrent chemoradiotherapy.

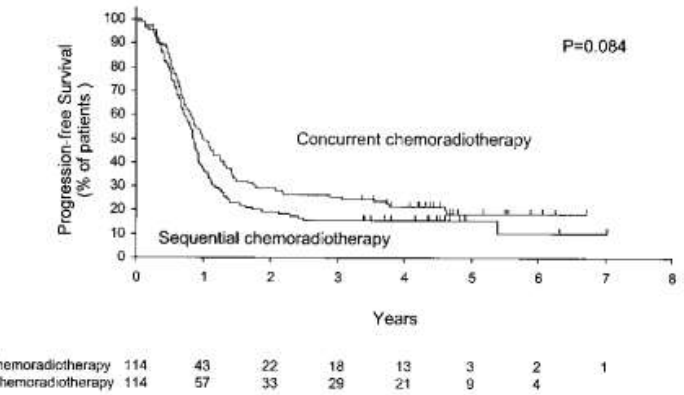


Fig 2. Progression-free survival of patients with LS-SCLC who were assigned to treatment with sequential chemoradiotherapy or concurrent chemoradiotherapy.

	Sequential	Concurrent
Median survival	19.7 months	27.2 months
2yr/3yr/5yr survival	35.1%/20.2%/18.3%	54.4%/29.8%/23.7%

Takada M et al . Clinical Oncology Group Study 9104. J Clin Oncol. 2002 Jul 15;20(14):3054-60

Table 2. Incidence of Toxic Effects According to Treatment Arm: Patients Assessable for Toxicity*

Toxic Effect/Grade	Sequential Arm (n = 110)		Concurrent Arm (n = 112)		
	No. of Patients	%	No. of Patients	%	*P*
Hematologic toxicity ≥ grade 3					
Leukopenia	59	54	99	88	< .001
Grade 3	49		57		
Grade 4	10		42		
Thrombocytopenia	29	26	41	37	.11
Grade 3	14		33		
Grade 4	15		8		
Anemia					
Grade 3	46	42	60	54	.08
Nonhematologic toxicity ≥ grade 3					
Nausea/vomiting	21	19	12	11	.09
Esophagitis	4	4	10	9	.17
Alopecia†	14	13	13	12	.99
Fever	2	2	2	2	.99
Infection	1	1	6	5	.12
Arrhythmias	0	0	2	2	.50
Treatment-related death	4	4	3	3	.72

*Data were not available for seven patients in the sequential arm and two patients in the concurrent arm.

†Data on alopecia were available for 109 patients in the sequential arm and 109 patients in the concurrent arm.

Takada M et al . Clinical Oncology Group Study 9104. J Clin Oncol. 2002 Jul 15;20(14):3054-60

If concurrent how early?

- Initiating RT 9 wks after the initiation of chemotherapy

  & before the third cycle of chemotherapy[1]

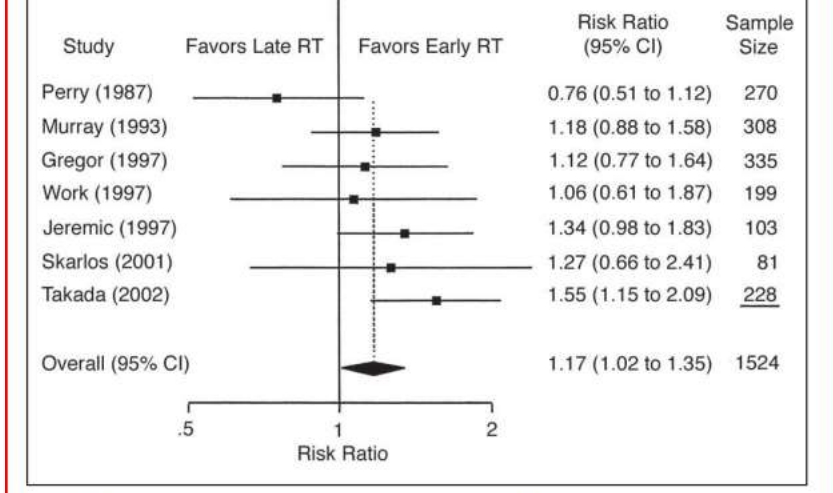


Fig 1. Two-year overall survival risk ratio forest plot for early *v* late thoracic radiation therapy (RT).

- The start of any treatment until the end of radiotherapy is an important predictor of outcome [2]
- Each week of extension of SER beyond that of the study arm with the shortest SER resulted in an overall absolute decrease in the 5-year survival rate of 1.83% 0.18% (95% CI) [2]

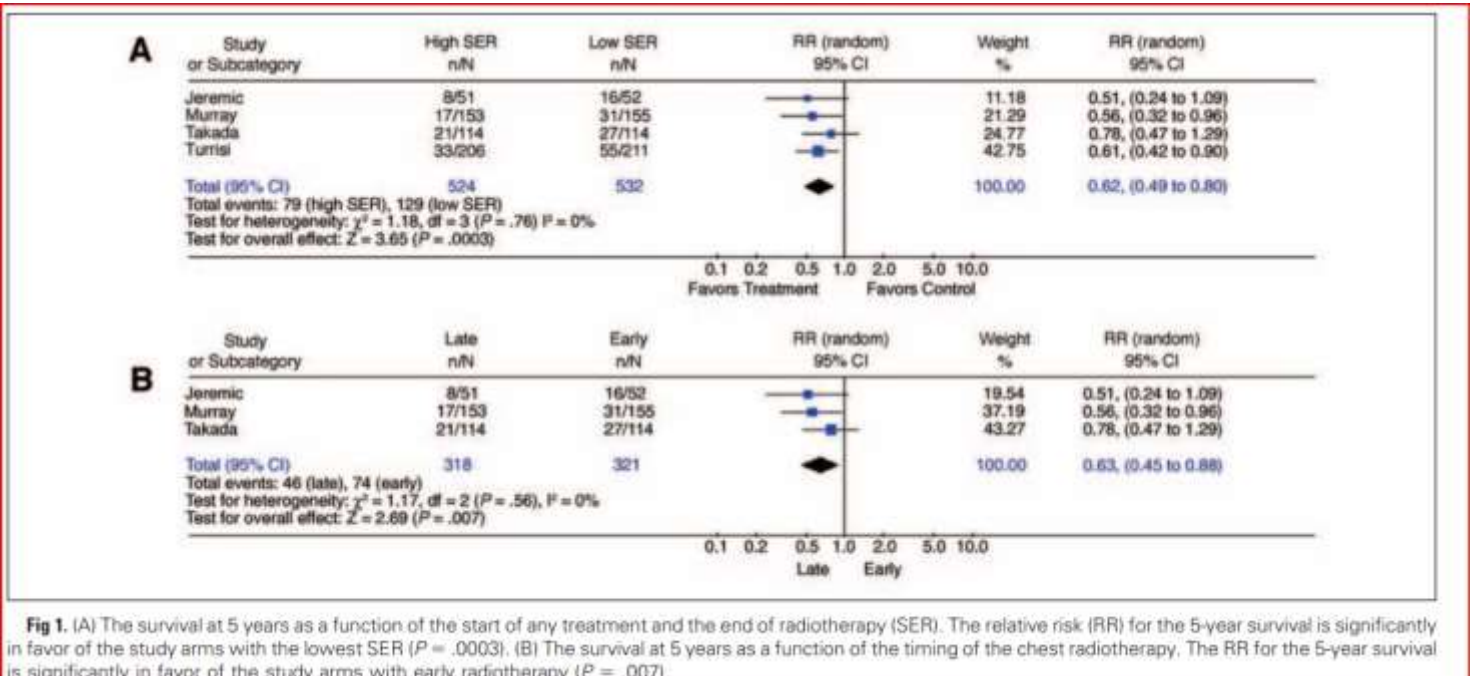


Fig 1. (A) The survival at 5 years as a function of the start of any treatment and the end of radiotherapy (SER). The relative risk (RR) for the 5-year survival is significantly in favor of the study arms with the lowest SER ($P = .0003$). (B) The survival at 5 years as a function of the timing of the chest radiotherapy. The RR for the 5-year survival is significantly in favor of the study arms with early radiotherapy ($P = .007$).

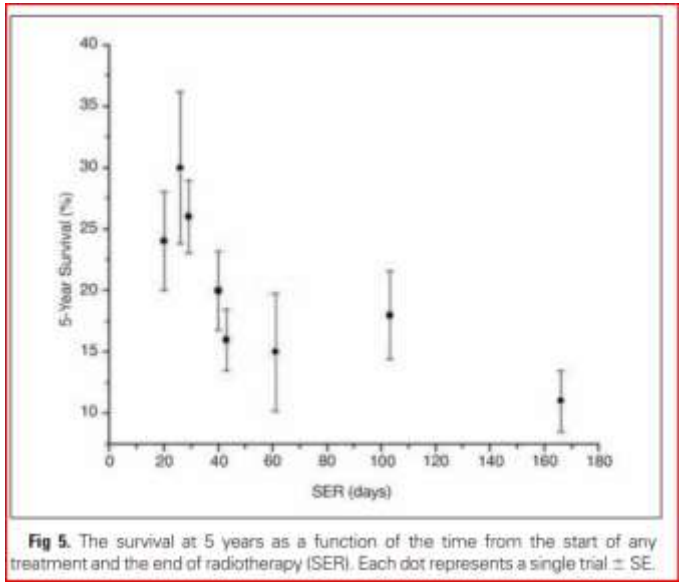


Fig 5. The survival at 5 years as a function of the time from the start of any treatment and the end of radiotherapy (SER). Each dot represents a single trial ± SE.

1.Fried DB et al. J Clin Oncol. 2004 Dec 1;22(23):4837-45

2. De Ruysscher D et al J Clin Oncol. 2006 Mar 1;24(7):1057-63

Principles of radiation therapy

LS – SCLC

- For patients starting systemic therapy before RT, limit the GTV to the post-therapy volume to reduce toxicity, covering the initially involved nodal regions
- Twice-daily radiotherapy (45 Gy in 3 weeks = 1.5 Gy BID) was superior compared to once-daily radiotherapy (45 Gy in 5 weeks = 1.8 Gy/day) [1] but was comparable to once-daily higher doses of radiation (66-70 Gy in 6.5-7 weeks = 2 Gy/day) [2]
- Had comparable side effect profile in BID vs higher dose OD dosing
- When BID is used interfraction interval should be at least 6 hrs

1. Turrisi AT et al. N Engl J Med. 1999 Jan 28;340(4):265-71
2. Faivre-Finn C et al. Lancet Oncol. 2017 Aug;18(8):1116-1125

Principles of radiation therapy

ES-SCLC – As a consolidative therapy

- Only in selected patients with good response to systemic therapy for residual thoracic and low bulk extrathoracic metastasis
- Dosing – individualized from 30 Gy in 10 daily fractions to definitive dosing regimens as described previously

Prophylactic cranial irradiation

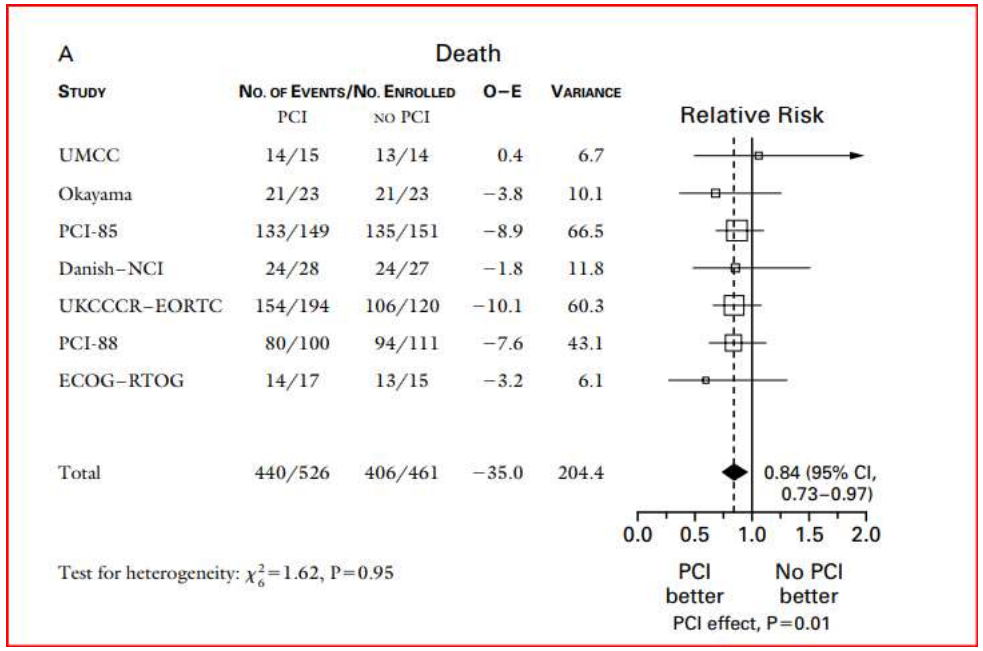
The New England Journal of Medicine

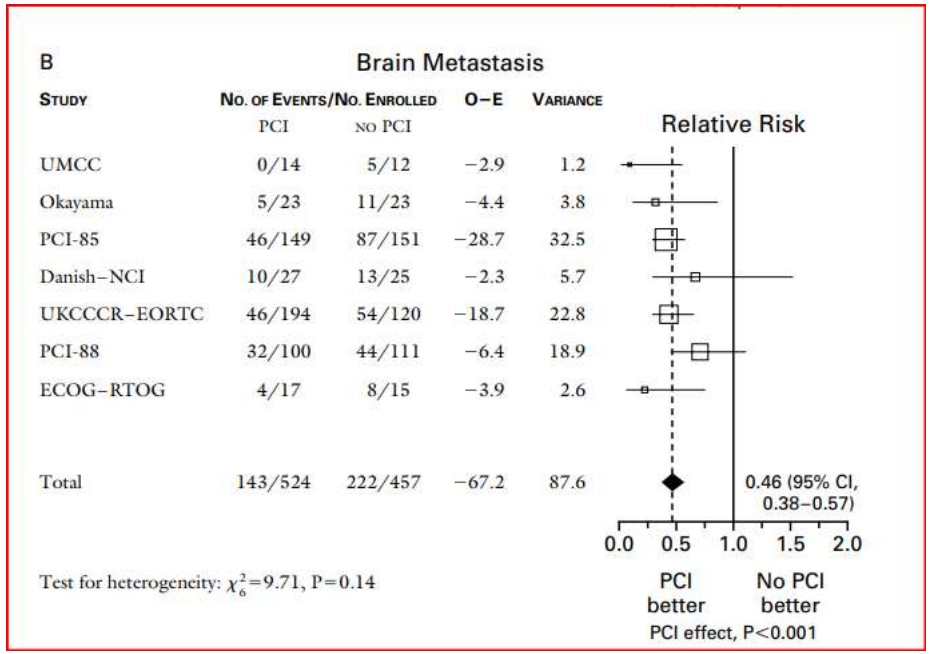
PROPHYLACTIC CRANIAL IRRADIATION FOR PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION

ANNE AUPÉRIN, M.D., RODRIGO ARRIAGADA, M.D., JEAN-PIERRE PIGNON, M.D., PH.D., CÉCILE LE PÉCHOUX, M.D., ANNA GREGOR, M.D., RICHARD J. STEPHENS, PAUL E.G. KRISTJANSEN, M.D., PH.D., BRUCE E. JOHNSON, M.D., HIROSHI UEOKA, M.D., HENRY WAGNER, M.D., AND JOSEPH AISNER, M.D., FOR THE PROPHYLACTIC CRANIAL IRRADIATION OVERVIEW COLLABORATIVE GROUP*

LS-SCLC with good response to initial treatment

- PCI decreases brain metastasis and increases overall survival
- 7 trials – 987 patients





- Relative risk of death = 0.84 --- 5.4% increase in rate of survival at 3 yrs
- Increased rate of disease-free survival – relative risk is 0.75

Aupérin A et al. N Engl J Med. 1999 Aug 12;341(7):476-84

TABLE 3. RESULTS OF THE META-ANALYSIS OF PROPHYLACTIC CRANIAL IRRADIATION IN PATIENTS WITH SMALL-CELL LUNG CANCER IN COMPLETE REMISSION.*

END POINT	NO. OF PATIENTS		RELATIVE RISK (95% CI)	P VALUE	HETEROGENEITY (P VALUE)	RATE IN THE CONTROL GROUP OVER A 3-YR PERIOD	ABSOLUTE BENEFIT AT 3 YR
	TREATMENT GROUP	CONTROL GROUP					
						percent	
Overall survival	526	461	0.84 (0.73–0.97)	0.01	0.95	15.3	+5.4
Disease-free survival	526	461	0.75 (0.65–0.86)	<0.001	0.96	13.5	+8.8
Cumulative incidence of brain metastasis	524	457	0.46 (0.38–0.57)	<0.001	0.14	58.6	−25.3
Cumulative incidence of other metastases	325	332	0.89 (0.69–1.15)	0.37	0.51	45.6	−3.8
Cumulative incidence of local or regional recurrence	323	334	0.97 (0.75–1.26)	0.84	0.45	45.1	−1.0

TABLE 4. INDIRECT AND SUBGROUP ANALYSES.*

CHARACTERISTIC	NO. OF PATIENTS		RELATIVE RISK OF DEATH (95% CI)	P VALUE		RELATIVE RISK OF BRAIN METASTASIS (95% CI)	P VALUE	
	TREATMENT GROUP (N=526)	CONTROL GROUP (N=461)		INTERACTION	TREND		INTERACTION	TREND
Total dose of cranial irradiation†				0.89	0.81		0.11	0.02
8 Gy	26	16	0.69 (0.35–1.37)			0.76 (0.28–2.10)		
24–25 Gy	330	340	0.88 (0.75–1.04)			0.52 (0.41–0.67)		
30 Gy	119	82	0.81 (0.59–1.12)			0.34 (0.19–0.59)		
36–40 Gy	51	59	0.81 (0.54–1.20)			0.27 (0.14–0.51)		
Sex				0.07			0.87	
Male	403	352	0.77 (0.66–0.90)			0.45 (0.36–0.58)		
Female	123	109	1.05 (0.78–1.42)			0.47 (0.31–0.74)		
Age				0.74	0.75		0.41	0.20
<55 yr	147	158	0.84 (0.65–1.02)			0.55 (0.39–0.77)		
55–64 yr	250	185	0.90 (0.73–1.11)			0.49 (0.35–0.68)		
>65 yr	129	118	0.79 (0.60–1.03)			0.37 (0.24–0.59)		
Performance status‡				0.62			0.82	
0	212	215	0.85 (0.69–1.05)			0.47 (0.35–0.63)		
1–3	103	111	0.78 (0.58–1.04)			0.50 (0.32–0.78)		
Initial disease				0.62			0.42	
Limited	464	383	0.85 (0.73–0.99)			0.48 (0.38–0.60)		
Extensive	62	78	0.77 (0.54–1.11)			0.38 (0.23–0.64)		
Induction therapy§				0.88			0.76	
Chemotherapy plus thoracic radiotherapy	314	248	0.86 (0.71–1.03)			0.43 (0.33–0.57)		
Chemotherapy without thoracic radiotherapy	94	86	0.88 (0.64–1.21)			0.40 (0.23–0.67)		
Time between start of induction therapy and randomization¶				0.46	0.39		0.03	0.01
<4 mo	84	77	0.92 (0.66–1.29)			0.27 (0.16–0.46)		
4–6 mo	127	152	0.79 (0.61–1.02)			0.50 (0.35–0.72)		
>6 mo	102	91	1.01 (0.74–1.38)			0.69 (0.44–1.08)		

Aupérin A et al. N Engl J Med. 1999 Aug 12;341(7):476-84

Prophylactic cranial irradiation

Research Paper

Prophylactic cranial irradiation in resected small cell lung cancer: A systematic review with meta-analysis

Yang Yang, Danhong Zhang, Xia Zhou, Wuan Bao, Yonglin Ji, Liming Sheng, Lei Cheng, Ying Chen, Xianghui Du, Guoqin Qiu

Very early LS-SCLC with complete resection of primary

- PCI is beneficial in all resected patients but not in p-stage I tumors
- 4 retrospective studies studying the effect of PCI in resected SCLC and 6 studies reporting the incidence of BM incidence in p-stage I patients but no radiology used (CT/MRI)
- 1691 patients (315 received PCI)

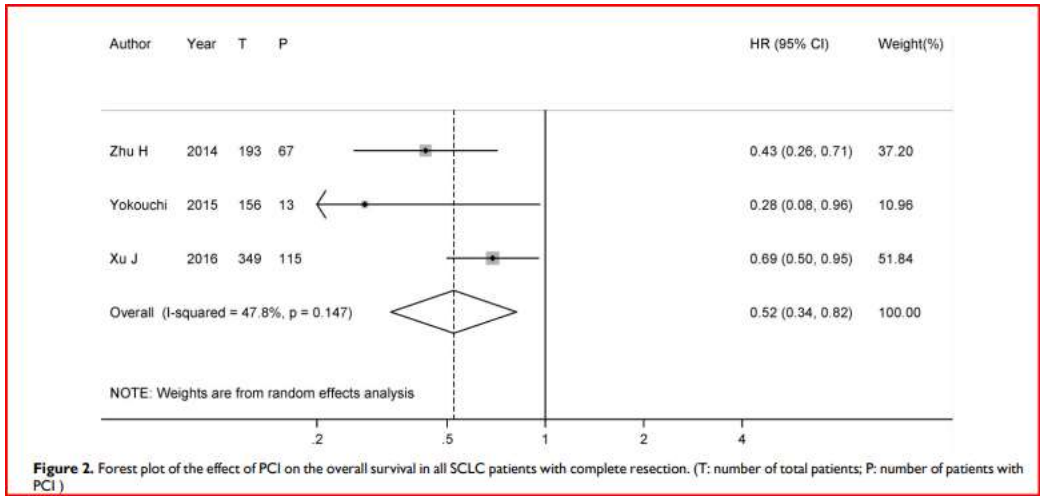


Figure 2. Forest plot of the effect of PCI on the overall survival in all SCLC patients with complete resection. (T: number of total patients; P: number of patients with PCI)

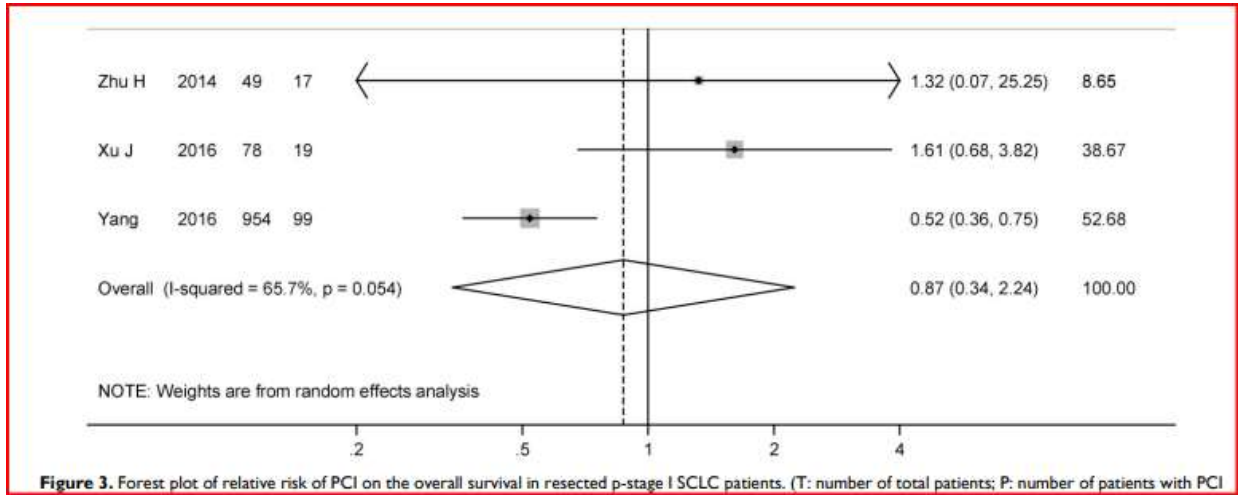


Figure 3. Forest plot of relative risk of PCI on the overall survival in resected p-stage I SCLC patients. (T: number of total patients; P: number of patients with PCI

- Reduced brain metastasis risk in completed resected SCLC except for p-stage I patients

MRI surveillance is recommended for patients not receiving PCI

May benefit patients with p-stage II or III (irrespective of imaging)

Yang Y et al. J Cancer. 2018 Jan 1;9(2):433-439

Prophylactic cranial irradiation - ES-SCLC

Slotman et al.	18-75 yrs ES- SCLC ECOG PS 0-2 Responded to chemotherapy Interval < 5 wks of last cycle No neuroimaging before symptoms	2 Groups PCI vs No PCI 143 each	Endpoint – time to symptomatic brain metastasis	Irradiation group – lower risk of brain metastasis (hazard ratio – 0.27) Risk of brain mets - 14.6% vs 40.4% Median DFS – 14.7 vs 12 weeks Median OS – 6.7 vs 5.4 months 1 yr survival – 27.1% vs 13.3% HR for death – 0.68
Takahashi et al.	>20 yrs ES – SCLC ECOG PS 0-2 Response assessment after 2# Absence of brain metastasis confirmed by CE-MRI within 4 weeks of enrolment Absence of tumor regrowth confirmed by CECT	2 Groups PCI vs No PCI 113 vs 111 The planned sample was 330 but was terminated early	Endpoint – OS	At 1st interim analysis 84 vs 79 – 73% vs 63% died with Median OS 10.1 vs 15.1 months Final 224 enrolled (113 vs 111) Median OS – 11.6 vs 13.7 months No significant benefit in OS/ incidence of brain metastasis or PFS

Slotman B et al. N Engl J Med. 2007 Aug 16;357(7):664-72
Takahashi T et al Lancet Oncol. 2017 May;18(5):663-671

Table 2. Scores on Quality-of-Life Assessment.*

Quality-of-Life Score	Assessment Time	Prophylactic Cranial Irradiation	Control	P Value†
Primary end points				
Global health status	0–9 mo‡			0.10
Role functioning	0–9 mo‡			0.17
Cognitive functioning	0–9 mo‡			0.07
Emotional functioning	0–9 mo‡			0.18
Fatigue	6 wk	43.2±2.56	29.3±2.47	<0.001
	3 mo	53.6±3.03	38.5±3.24	<0.001
Hair loss	6 wk	36.5±3.96	11.7±3.73	<0.001
Exploratory results				
Appetite loss	6 wk	28.9±3.25	10.6±3.06	<0.001
	3 mo	43.9±3.87	14.8±4.18	<0.001
Nausea and vomiting	6 wk	15.0±1.73	5.3±1.64	<0.001
	3 mo	26.9±2.92	8.2±3.15	<0.001
Leg weakness	6 wk	25.2±2.71	11.8±2.48	<0.001
	3 mo	32.2±3.62	16.0±3.93	0.003

MRI surveillance is recommended for patients irrespective of PCI

	Prophylactic cranial irradiation (n=106)				Observation (n=111)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Alopecia	21 (20%)	24 (23%)	0	0	24 (22%)	16 (14%)	0	0
Dermatitis	17 (16%)	3 (3%)	1 (<1%)	1 (<1%)	3 (3%)	0	0	0
Headache	7 (7%)	0	0	0	3 (3%)	0	0	0
Anorexia	33 (31%)	10 (9%)	5 (5%)	1 (<1%)	14 (13%)	5 (5%)	2 (2%)	0
Nausea	25 (24%)	6 (6%)	2 (2%)	0	8 (7%)	1 (<1%)	0	0
Vomiting	7 (7%)	1 (<1%)	0	0	0	1 (<1%)	0	0
Dizziness	5 (5%)	2 (2%)	1 (<1%)	0	3 (3%)	0	0	0
Malaise	28 (26%)	7 (7%)	3 (3%)	0	21 (19%)	3 (3%)	0	1 (<1%)
Lethargy	6 (6%)	1 (<1%)	1 (<1%)	0	2 (2%)	1 (<1%)	0	0
Muscle weakness (lower limb)	3 (3%)	3 (3%)	1 (<1%)	0	1 (<1%)	0	5 (5%)	1 (<1%)

Table 2: **Adverse events at 3 months after randomisation**

Slotman B et al. N Engl J Med. 2007 Aug 16;357(7):664-72
Takahashi T et al Lancet Oncol. 2017 May;18(5):663-671

PCI – dose and when to administer?

- Preferred PCI dose is 25 Gy in 10 daily fractions - not recommended in poor PS and impaired cognition
- Shorter courses (e.g., 20 Gy in 5 fractions) - for extensive-stage disease
- Higher doses (e.g., 36 Gy) increase mortality and chronic neurotoxicity [1]

- Administer PCI after resolving acute toxicities from initial therapy

- To prevent neurocognitive impairment
  - Doubtful role of memantine
  - Doubtful role of hippocampal avoidance PCI

Le Péchoux C et al Lancet Oncol. 2009 May;10(5):467-74

Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study

Phase III trial with 150 SCLC patients (71.3% with limited disease) randomized to standard PCI (25 Gy in 10 fractions) or HA-PCI.

Primary endpoint: Delayed free recall (DFR) decline on the Free and Cued Selective Reminding Test (FCSRT) at 3 months.

Secondary endpoints: Other FCSRT scores, quality of life (QoL), brain metastases incidence, and OS.

Results:

Cognitive Function:

- DFR decline at 3 months: 5.8% (HA-PCI) vs. 23.5% (PCI)
- Declines in total recall (TR) and other FCSRT scores were consistently lower in the HA-PCI group at 3, 6, and 24 months.

- Brain Metastases, OS, and QoL:
  - No significant differences between HA-PCI and PCI groups

Rodríguez de Dios N et al. J Clin Oncol. 2021 Oct 1;39(28):3118-3127

Treatment Planning Parameters		
Hippocampus, cc		
Mean (SD)	4.5 (2.5)	4.5 (2.4)
Median (q1, q3)	3.8 (3.0, 5.7)	4.1 (3.1, 5.0)
Min-max	1.1-12.7	1.5-16.1
No. (% nonmissing)	68 (100.0)	69 (100.0)
HAZ, cc		
Mean (SD)	28.6 (8.0)	30.2 (7.6)
Median (q1, q3)	27.0 (23.5, 33.0)	28.7 (24.9, 34.1)
Min-max	12.9-49.5	13.7-59.2
No. (% nonmissing)	68 (100.0)	69 (100.0)
Mean dose hippocampus, Gy		
Mean (SD)	24.5 (2.1)	10.9 (2.0)
Median (q1, q3)	24.8 (24.4, 25.1)	11.6 (9.7, 12.4)
No. (% nonmissing)	68 (100.0)	69 (100.0)
Dmax hippocampus, Gy		
Mean (SD)	24.9 (1.7)	14.7 (2.7)
Median (q1, q3)	25.0 (24.7, 25.4)	16.0 (13.9, 16.7)
No. (% nonmissing)	68 (100.0)	69 (100.0)
D100% hippocampus, Gy		
Mean (SD)	24.2 (2.1)	8.5 (1.3)
Median (q1, q3)	24.4 (24.1, 24.8)	8.7 (7.5, 9.2)
No. (% nonmissing)	68 (100.0)	69 (100.0)

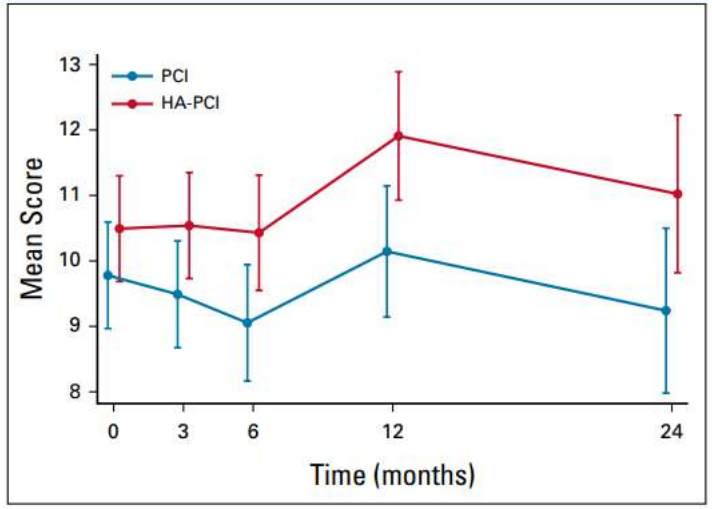


FIG 2. Mean scores of FCSRT-delayed free recall over time. FCSRT, Free and Cued Selective Reminding Test. HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

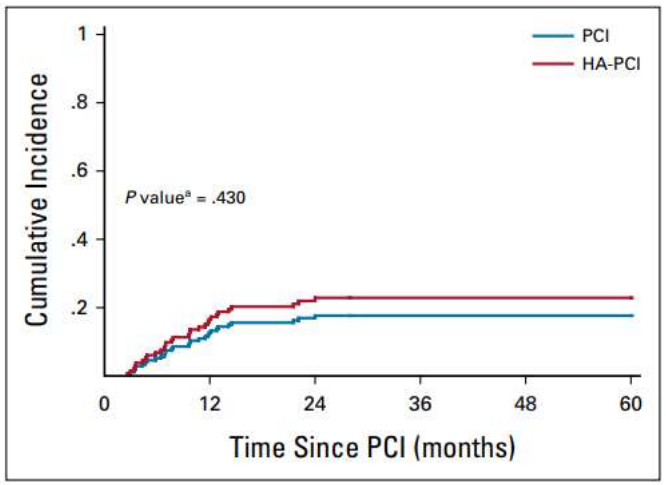


FIG 3. Cumulative incidence of brain metastases. [a]Pepe and Mori test comparing the cumulative incidence of two groups of arm. HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

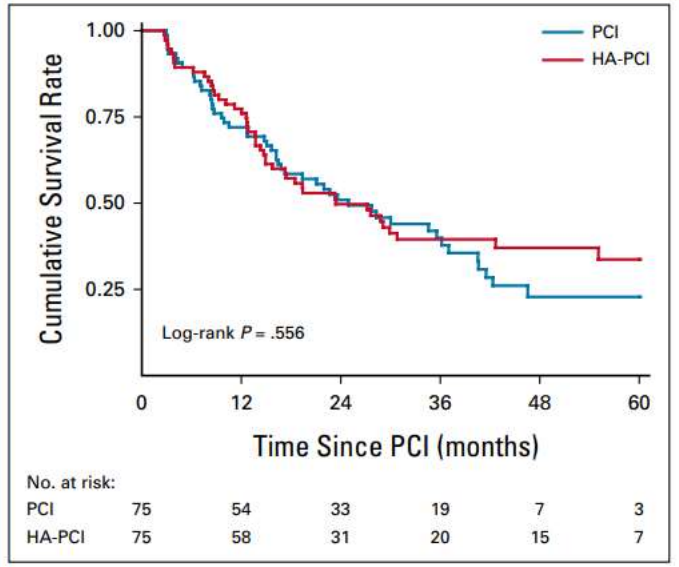


FIG 5. Overall survival for all randomly assigned patients. HA, hippocampal avoidance; PCI, prophylactic cranial irradiation.

Role of radiotherapy in metastasis

Brain metastasis – (Limited data)

- WBRT (30 Gy in 10 daily fractions) +/- Memantine
- Small number of metastasis – SRT/SRS can be tried (no data to support)
- Brain metastasis after PCI – repeat WBRT in carefully selected patients
- Patients with better prognosis – hippocampal sparing WBRT preferred (not preferred within 5 mm of the hippocampus, leptomeningeal metastasis)

As Palliation in extracranial metastasis

- Can be 30 Gy in 10 fractions, 20 Gy in 5 fractions
- Can use IMRT/SABR/SRS based on the number, and proximity of the tumor to organs at risk

Systemic therapy

- 1940s: Chemosensitivity was first identified with nitrogen mustard - tumor regression > 50% of patients
- 1969: Green et al demonstrated a statistically significant survival benefit with cyclophosphamide
- 1970s: Combination chemotherapy produced superior survival compared to single-agent treatment
- Late 1970s - Early 1980s: Cyclophosphamide-based regimens, such as CAV were commonly used.
- Mid-1980s: Induction regimens began incorporating etoposide, either with cisplatin or carboplatin, or as a substitute for components of the CAV regimen.
- 1980s: Randomized trials showed regimens containing etoposide yielded slightly superior survival compared to those without etoposide, though EP (cisplatin/etoposide) did not show a clear survival advantage over CAV in patients with extensive disease but showed benefit in limited disease [1]
- Since then etoposide and platinum-based chemotherapy became of standard of treatment

Haddadin S et al Clin Lung Cancer. 2011 Mar;12(2):87-93
1 - Sundstrøm S et al. J Clin Oncol. 2002 Dec 15;20(24):4665-72

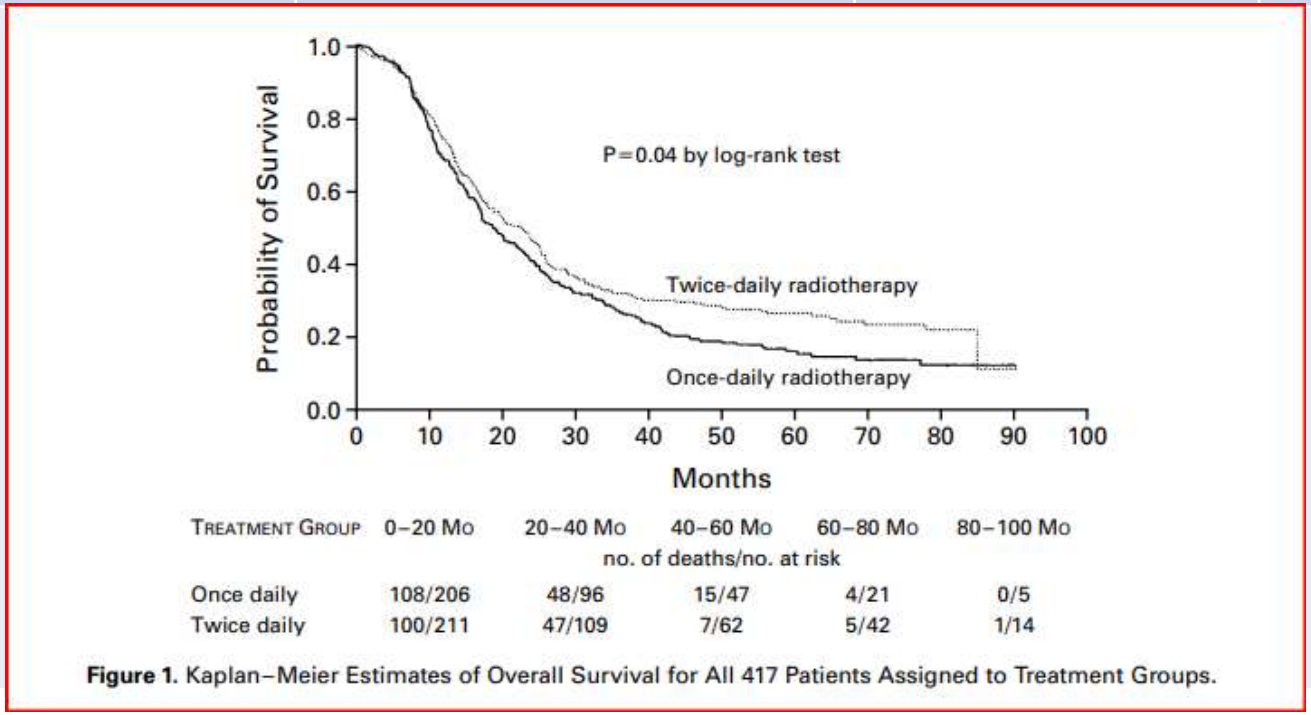
Systemic therapy – LS-SCLC

- Four cycles of cisplatin/etoposide is recommended
- Planned cycle length should be every 21–28 days during concurrent RT
- Use of myeloid growth factors is not recommended during concurrent chemoradiotherapy

Dosing regimens

- Cisplatin 75mg/m2 day 1 followed by etoposide 100 mg/m2 day 1,2,3
- Cisplatin 60mg/m2 day 1 followed by etoposide 120 mg/m2 day 1,2,3

	Population	Intervention	End point	
Andrew T. Turirssi et al. May 89 – July 92	LS – SCLC Staging by CT/ MRI/ radionucleotide bone scanning and b/l BM biopsy Adequate organ function	4# of CP 60mg & E 120mg Radiotherapy OD – 1.8 Gy 25# over 5 wk BD – 1.5 Gy 30# over 3 wk PCI – last 12 wks 10 # of 2.5 Gy over 2 wks	1^0 - OS	Median survival was OD vs BD – 19 vs 23 months 2 yr and 5 yr survival OD – 41% & 16% BD - 47% & 26% Total – 44% & 23%



Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

Figure 1. Kaplan–Meier Estimates of Overall Survival for All 417 Patients Assigned to Treatment Groups.

TABLE 2. TREATMENT COMPLICATIONS ACCORDING TO THE FREQUENCY OF RADIOTHERAPY.*

COMPLICATION AND NO. OF RADIATION TREATMENTS PER DAY	GRADE						P VALUE
	0	1	2	3	4	5	
	number (percent) of patients						
Overall†							0.80
1	1 (0.5)	3 (1)	20 (10)	47 (23)	127 (63)	5 (2)	
2	2 (1)	0	19 (9)	51 (25)	128 (62)	6 (3)	
Myelotoxicity‡							0.70
1	2 (1)	9 (4)	19 (9)	43 (21)	129 (64)	1 (0.5)	
2	7 (3)	2 (1)	18 (9)	52 (25)	127 (62)	0	
Esophagitis							<0.001
1	113 (56)	19 (9)	38 (19)	22 (11)	11 (5)	0	
2	76 (37)	26 (13)	37 (18)	56 (27)	11 (5)	0	
Other toxic effects							0.20
1	4 (2)	18 (9)	119 (59)	46 (23)	12 (6)	4 (2)	
2	2 (1)	13 (6)	119 (58)	53 (26)	13 (6)	6 (3)	

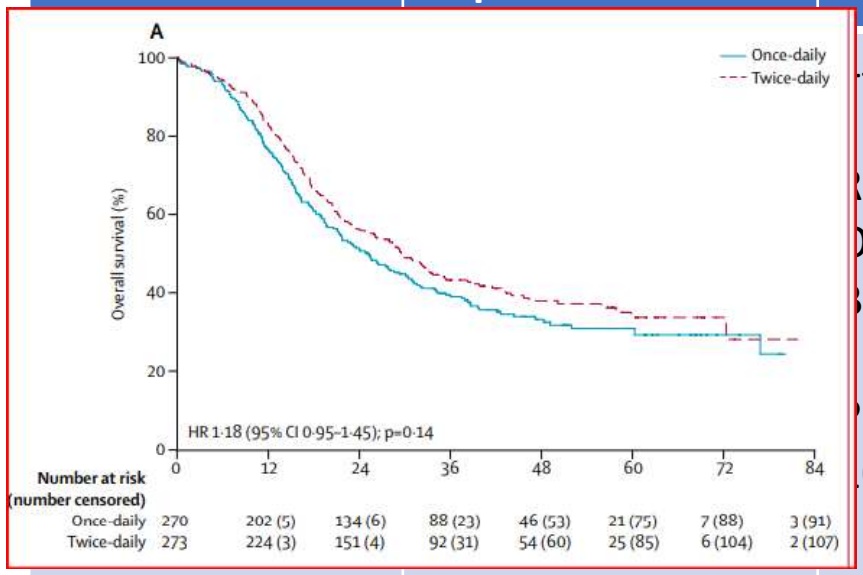
TABLE 3. INCIDENCE OF TOXIC EFFECTS ACCORDING TO THE FREQUENCY OF RADIOTHERAPY.*

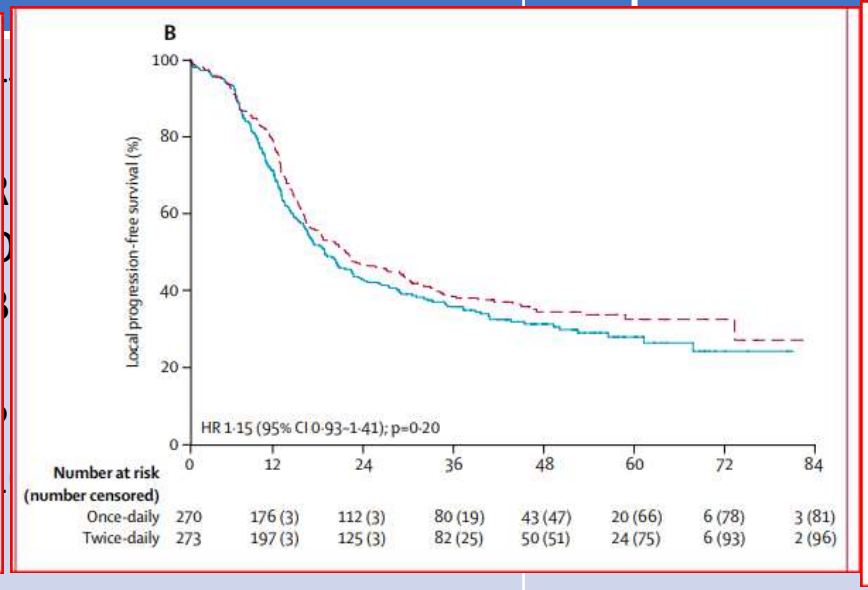
TOXIC EFFECT AND NO. OF RADIATION TREATMENTS PER DAY	GRADE					P VALUE
	1	2	3	4	5	
	number (percent) of patients					
Hematologic effects						
Leukopenia†						0.35
1	11 (5)	25 (12)	84 (41)	79 (39)	0	
2	2 (1)	26 (13)	79 (38)	90 (44)	0	
Granulocytopenia‡						0.75
1	11 (5)	15 (7)	31 (15)	122 (60)	0	
2	4 (2)	16 (8)	44 (21)	122 (59)	0	
Thrombocytopenia						0.83
1	47 (23)	30 (15)	32 (16)	16 (8)	0	
2	68 (33)	23 (11)	27 (13)	16 (8)	0	
Anemia						0.93
1	32 (16)	87 (43)	46 (23)	6 (3)	0	
2	38 (18)	79 (38)	47 (23)	10 (5)	0	
Infection						0.10
1	3 (1)	22 (11)	12 (6)	2 (1)	2 (1)	
2	5 (2)	34 (16)	12 (6)	4 (2)	2 (1)	
Fever						0.25
1	33 (16)	44 (22)	0	0	0	
2	47 (23)	46 (22)	0	0	0	
Vomiting						0.11
1	58 (29)	63 (31)	16 (8)	5 (2)	0	
2	50 (24)	55 (27)	17 (8)	3 (1)	0	
Pulmonary effects						0.97
1	18 (9)	13 (6)	6 (3)	1 (0.5)	1 (0.5)	
2	10 (5)	14 (7)	9 (4)	2 (1)	3 (1)	
Weight loss						0.05
1	65 (32)	47 (23)	6 (3)	0	0	
2	63 (30)	69 (33)	4 (2)	0	0	

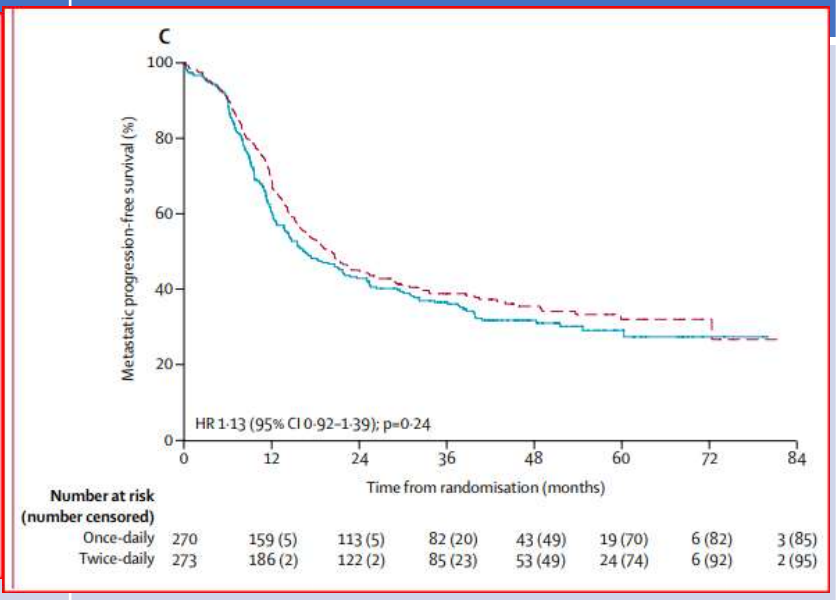
90% in both groups had myelosuppression – only one death due to it but no growth factors were used
A significant difference in esophagitis – 44% vs 63%

	Population	Intervention	End point	
Andrew T. Turirssi et al. May 89 – July 92	LS – SCLC Staging by CT/ MRI/ radionucleotide bone scanning and b/l BM biopsy Adequate organ function	4# of CP 60mg & E 120mg Radiotherapy OD – 1.8 Gy 25# over 5 wk BD – 1.5 Gy 30# over 3 wk PCI – last 12 wks 10 # of 2.5 Gy over 2 wks	1^0 – OS 206 vs 211	Median survival was OD vs BD – 19 vs 23 months 2 yr and 5 yr survival OD – 41% & 16% BD - 47% & 26% Total – 44% & 23%
Corinne Faivre-Finn et al. April 08- Nov 13	LS – SCLC ECOG PS 0-2 Stable biochemical parameters CT thorax abdomen, MRI PET +/-	4-6 # CP 75mg & E 100mg Radiotherapy OD – 2 Gy 33# over 45 days (66 Gy) BD – 1.5 Gy twice daily over 19 days (45 Gy) CCRT – radiotherapy with the second cycle PCI – within 6 wks of last cycle of chemo with no clinical evidence	1^0 – OS 2^0 – compliance, toxicity, PFS 273 vs 274	Median OS OD vs BD – 25 vs 30 months 2 yr OS OD – 51% BD – 56%

	Population	Intervention	End point	
Corinne Faivre-Finn et al. April 08- Nov 13	LS – SCLC ECOG PS 0-2 Stable biochemical parameters CT thorax abdomen, MRI PET +/-	4-6 # CP 75mg & E 100mg Radiotherapy OD – 2 Gy 33# over 45 days (66 Gy) BD – 1.5 Gy twice daily over 19 days (45 Gy) CCRT – radiotherapy with the second cycle PCI – within 6 wks of last cycle of chemo with no clinical evidence	1^0 – OS 2^0 – compliance, toxicity, PFS 273 vs 274	Median OS OD vs BD – 25 vs 30 months 2 yr OS OD – 51% BD – 56%







	Twice-daily group				Once-daily group				p value
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	
Adverse events in the population assessed for chemotherapy toxicity (n=266 in the twice-daily group; n=263 in the once-daily group)									
Nausea	172 (65%)	23 (9%)	..	..	171 (65%)	26 (10%)	..	..	0·63
Vomiting	105 (40%)	13 (5%)	..	..	95 (36%)	13 (5%)	..	..	0·99
Mucositis	88 (33%)	3 (1%)	..	..	87 (33%)	5 (2%)	1 (<1%)	..	0·34
Fatigue	212 (80%)	31 (12%)	..	..	216 (82%)	31 (12%)	2 (1%)	..	0·77
Neuropathy (motor)	12 (5%)	1 (<1%)	..	..	15 (6%)	2 (1%)	..	..	0·62
Neuropathy (sensory)	63 (24%)	3 (1%)	1 (<1%)	1 (<1%)	61 (23%)	5 (2%)	..	..	>0·99
Infection	43 (16%)	27 (10%)	7 (3%)	..	52 (20%)	27 (10%)	2 (1%)	2 (1%)	0·52
Anaemia	194 (73%)	32 (12%)	1 (<1%)	..	184 (70%)	34 (13%)	1 (<1%)	..	0·72
Febrile neutropenia	NA	49 (18%)	13 (5%)	1 (<1%)	NA	38 (14%)	8 (3%)	3 (<1%)	0·13
Neutropenia	38 (14%)	68 (26%)	129 (49%)	..	47 (18%)	69 (26%)	101 (38%)	..	0·05
Anorexia	135 (51%)	18 (7%)	..	..	129 (49%)	21 (8%)	..	..	0·60
Other*	150 (57%)	65 (24%)	9 (3%)	1 (<1%)†	177 (67%)	44 (17%)	8 (3%)‡	1 (<1%)	0·02
Adverse events in the population assessed for radiotherapy toxicity (n=254 in the twice-daily group; n=246 in the once-daily group)									
Oesophagitis	159 (63%)	46 (18%)	1 (<1%)	..	135 (54%)	47 (19%)	..	..	0·85
Pneumonitis	51 (20%)	3 (1%)	1 (<1%)	1 (<1%)	49 (19%)	3 (1%)	1 (<1%)	2 (1%)	0·70

Management of cytopenia

Chemoradiotherapy With or Without Granulocyte-Macrophage Colony-Stimulating Factor in the Treatment of Limited-Stage Small-Cell Lung Cancer: A Prospective Phase III Randomized Study of the Southwest Oncology Group

By Paul A. Bunn, Jr, John Crowley, Karen Kelly, Mark B. Hazuka, Kristie Beasley, Christine Upchurch, and Robert Livingston

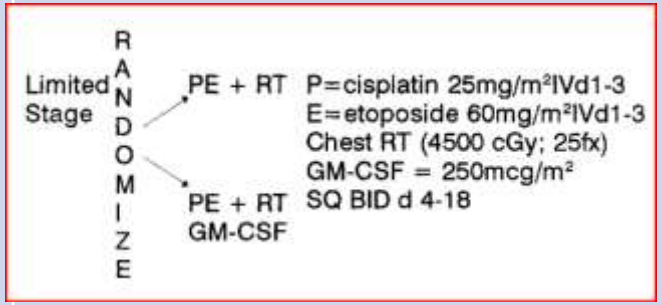
Population	Intervention	End point	
LS – SCLC Staging by CT/ MRI/ radionucleotide bone scanning and b/l BM biopsy Adequate organ function	 108 vs 107 patients	1^0 - Haematological toxicity 2^0 - fever, antibiotics, hospitalization, and infection	

Table 1. Clinical Features of Patients by Treatment Group

Feature	No GM-CSF (n = 108)	GM-CSF (n = 107)	P
Age, years			
Median	60	61	NS
Range	39-77	38-78	
Male/female	65/43	61/46	NS
White/nonwhite	100/8	97/10	NS
PS O-1/2	97/9	97/9	NS
Normal LDH/↑LDH	72/31	54/43	.04
Albumin ≥ 3.5/< 3.5	85/20	80/22	NS

Table 2. Hematologic Toxicity by Study Arm

Type of Toxicity	No GM-CSF (n = 108) No.	%	GM-CSF (n = 107) No.	%	P
WBC (grade)					
≥ 3	70	65	43	40	< .001
≥ 4	13	12	14	13	NS
Neutrophils (grade)					
≥ 3	62	57	49	46	NS
≥ 4	26	24	19	18	.01
Platelets (grade)					
≥ 3	13	12	58	54	< .001
≥ 4	6	6	37	35	< .001
Hemoglobin (grade)					
≥ 3	21	19	35	33	.03
≥ 4	4	4	6	6	NS

Management of cytopenia

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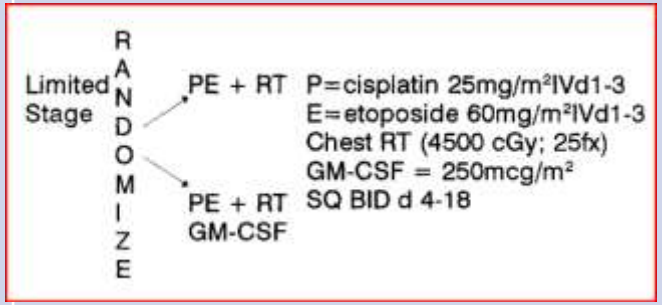
LS – SCLC Staging by CT/ MRI/ radionucleotide bone scanning and b/l BM biopsy Adequate organ function	 108 vs 107 patients	1^0 - Haematological toxicity 2^0 - fever, antibiotics, hospitalization, and infection	1. Increase in the frequency and duration of life-threatening thrombocytopenia 2. significantly more deaths 3. nonhematologic toxicities 4. more days in the hospital 5. higher incidence of IV antibiotic usage 6. more transfusions 7. No significant difference in the frequency of grade 4 leukopenia or neutropenia Lower CR(36% vs 44%) - not significant Median OS - 14 months vs 17 months (not significant)

Table 1. Clinical Features of Patients by Treatment Group

Feature	No GM-CSF (n = 108)	GM-CSF (n = 107)	P
Age, years			
Median	60	61	NS
Range	39-77	38-78	
Male/female	65/43	61/46	NS
White/nonwhite	100/8	97/10	NS
PS O-1/2	97/9	97/9	NS
Normal LDH/↑LDH	72/31	54/43	.04
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Table 2. Hematologic Toxicity by Study Arm

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≥ 3	70	65	43	40	< .001
≥ 4	13	12	14	13	NS
Neutrophils (grade)					
≥ 3	62	57	49	46	NS
≥ 4	26	24	19	18	.01
Platelets (grade)					
≥ 3	13	12	58	54	< .001
≥ 4	6	6	37	35	< .001
Hemoglobin (grade)					
≥ 3	21	19	35	33	.03
≥ 4	4	4	6	6	NS

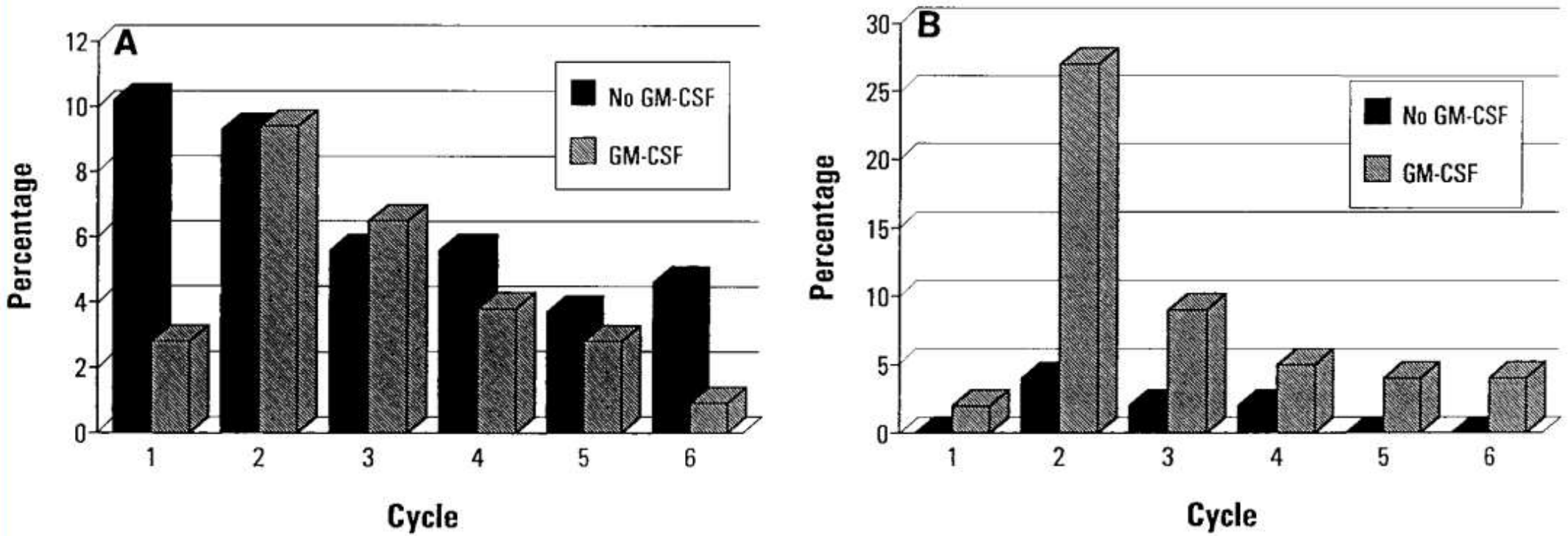
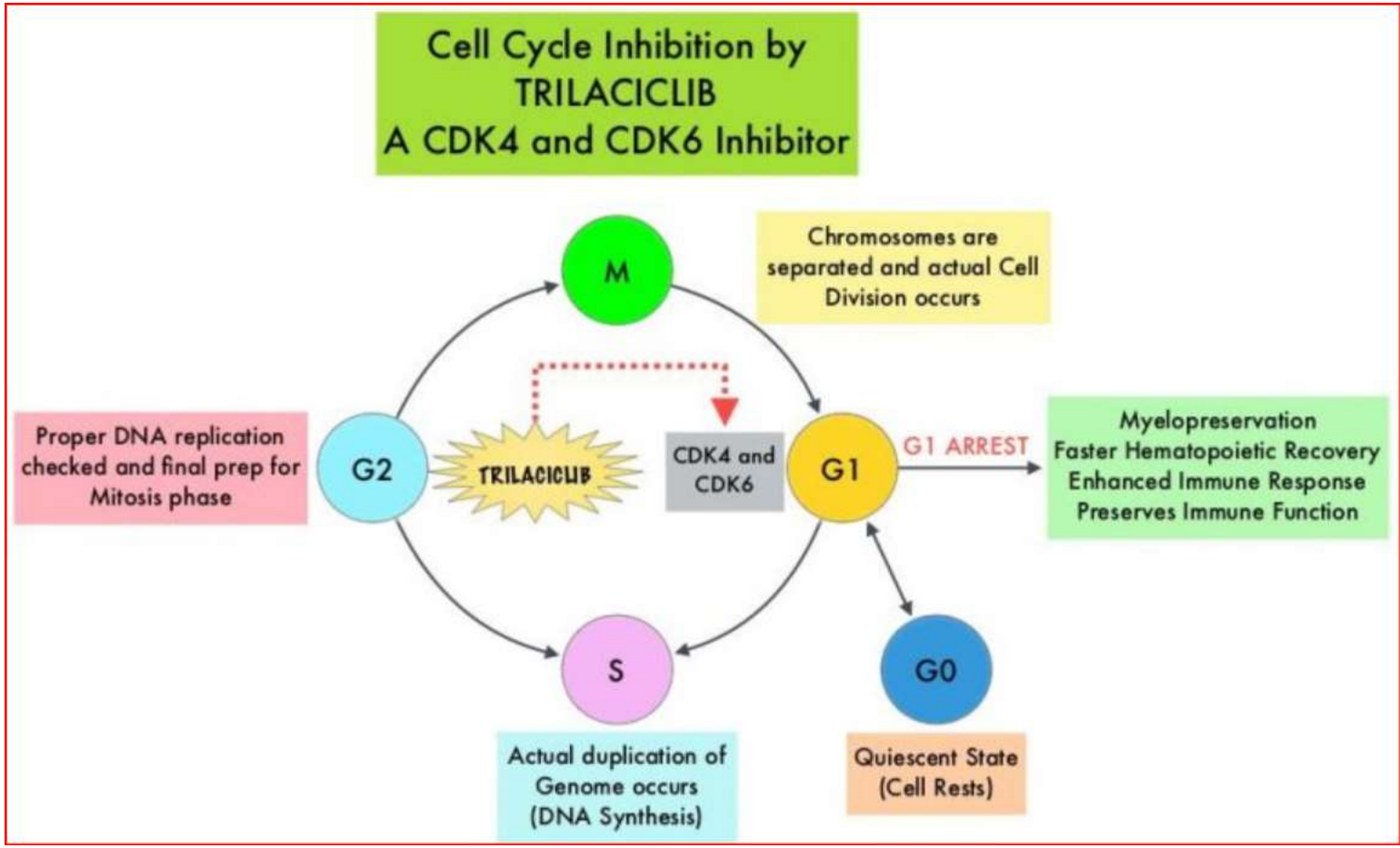


Fig 2. Hematologic toxicity by chemotherapy cycle for patients treated with or without GM-CSF. (A) Percentage of patients who develop grade 4 neutropenia during each cycle by study arm. (B) Percentage of patients who develop ≥ grade 4 thrombocytopenia by study arm.

Trilaciclib for myeloprotection

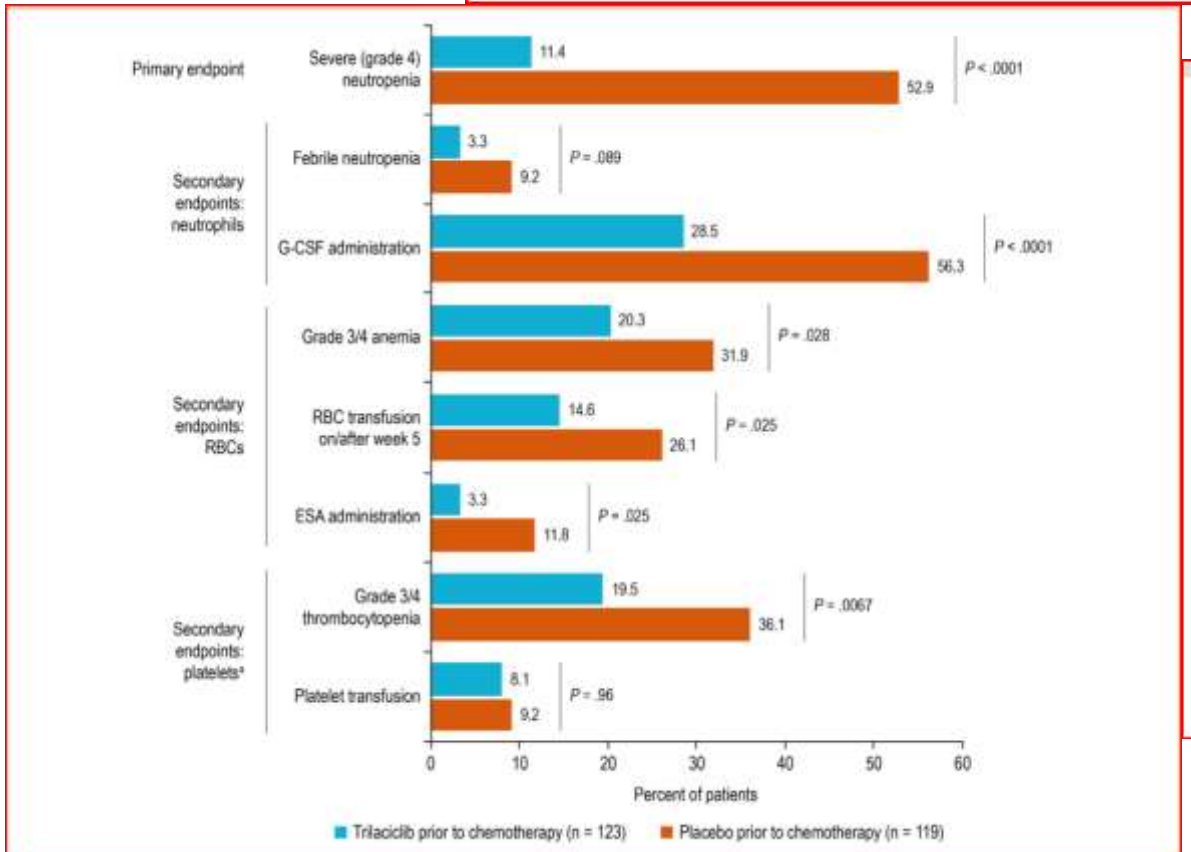
- **Cell Cycle Arrest**: administered 4 hrs before chemotherapy
- It arrests HSC at the G1 phase during chemotherapy by inhibiting CDK4/6, key regulators for cycle progression – protects cells from chemo-induced cytotoxicity (myeloprotection)
- SCLC tumor cells replicate independently of CDK4/6 thus not interfering with anti-tumor efficacy

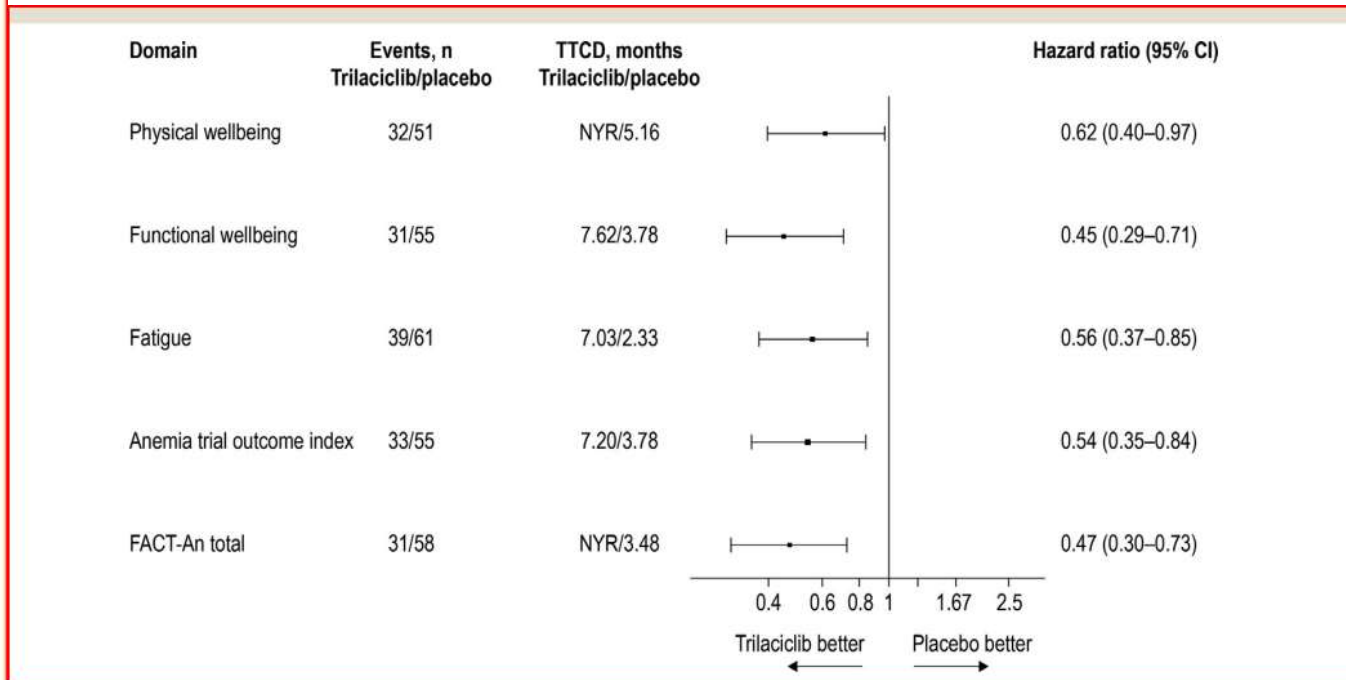


3 phase 2 RCTs

Table 1 Overview of Trilaciclib Clinical Studies Included in Pooled Analysis

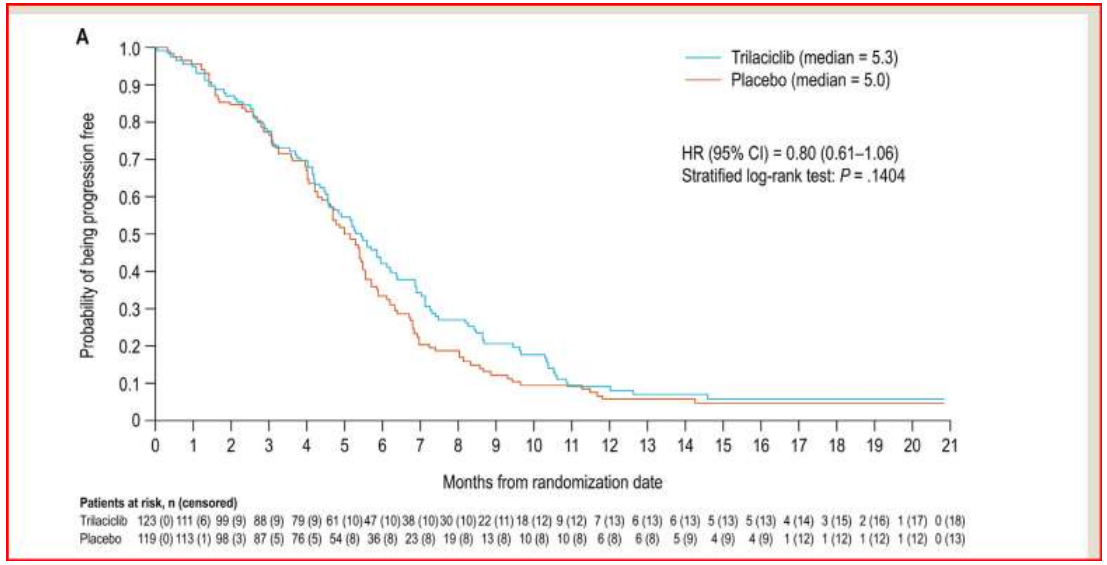
Study	Patient Population	Treatment Schedule
G1T28-05 (NCT03041311)	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to chemotherapy on days 1-3 of each 21-day E/P/A IV cycle[a] for up to four cycles followed by atezolizumab monotherapy (without trilaciclib) Q21D Placebo IV QD prior to chemotherapy on days 1-3 of each 21-day E/P/A IV cycle for up to four cycles followed by atezolizumab monotherapy (without placebo) Q21D
G1T28-02 (NCT02499770)	Newly diagnosed (first-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to chemotherapy on days 1-3 of each 21-day E/P IV cycle[b] Placebo IV QD prior to chemotherapy on days 1-3 of each 21-day E/P IV cycle
G1T28-03 (NCT02514447)	Previously treated (second-/third-line) ES-SCLC	Trilaciclib 240 mg/m^2 IV QD prior to topotecan 1.5 mg/m^2 IV QD on days 1-5 of each 21-day cycle Placebo IV QD prior to topotecan 1.5 mg/m^2 IV QD on days 1-5 of each 21-day cycle

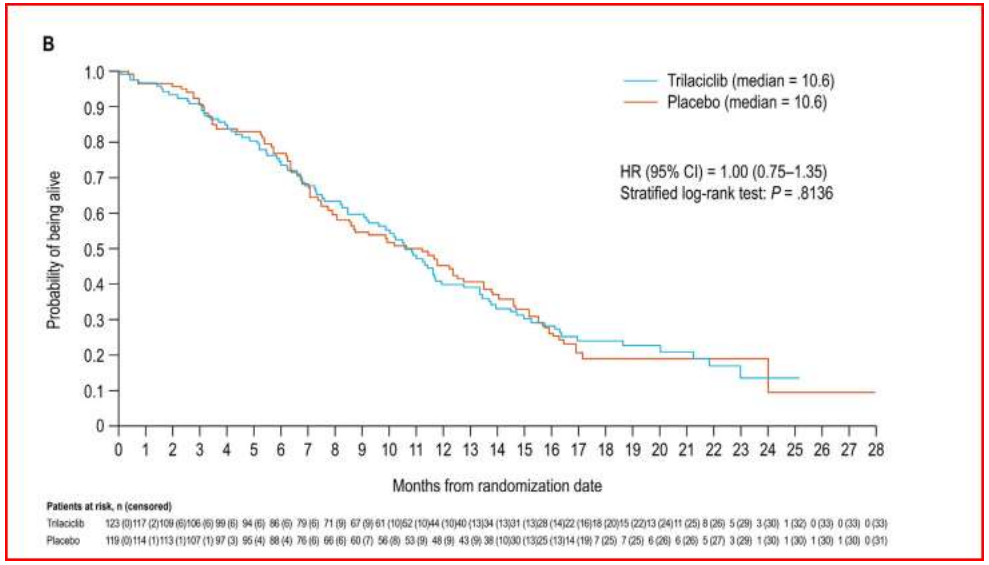




Weiss J et al. Clin Lung Cancer. 2021 Sep;22(5):449-460

No effect on OS and PFS





Adverse events –

- Injection site reactions (17%, no grade 3-4)
- Phlebitis (8%, 0.5% grade 3-4)
- Hypersensitivity (6%, no grade 3-4)

Weiss J et al. Clin Lung Cancer. 2021 Sep;22(5):449-460

Immunotherapy in LS-SCLC

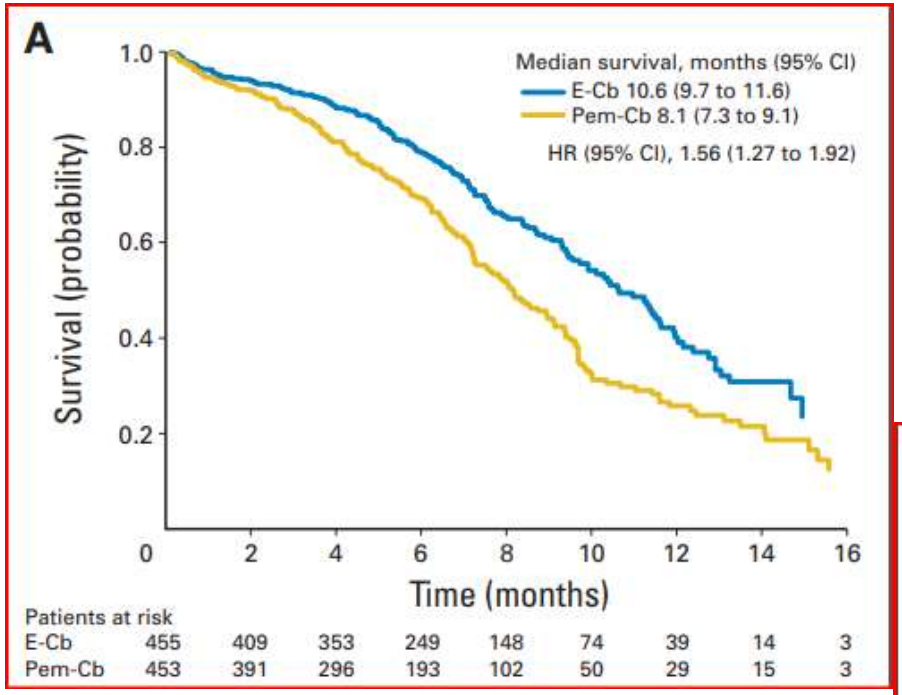
	Population	Intervention	End point	
Cheng et al	LS – SCLC ECOG PS 0/1 Received 4# EP concurrent with RT commenced no later than the end of 2# with CR/PR/SD Adequate organ function PCI if applicable	Durvalumab 1500 Q4wk vs placebo Q4wk Blinded data of tremelimumab arm	1^0 – OS, PFS 2^0 – OS at 24/36 months, adverse events, OR and PFS at 18 and 24 months	Median OS – 55.9 vs 33.4 months Hazards ratio 0.73 (p=0.01) Median PFS – 16.6 vs 9.2 months HR – 0.76 (P=0.02) 2 yr and 3 yrs OS D – 68% & 56.5% P – 58.5% & 47.6% 18 months and 24 months PFS D – 48.8% & 46.2% P – 36.1% & 34.2%

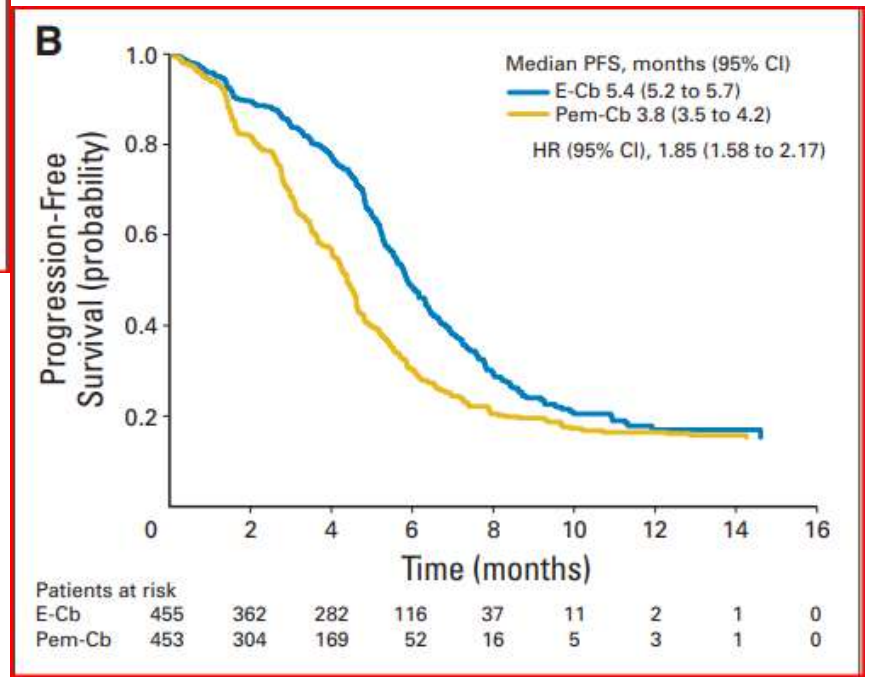
CONSOLIDATION WITH DURVALUMAB AFTER CCRT IS RECOMMENDED

Systemic therapy – ES-SCLC

	Population	Intervention	End point	
Mark A. Socinski et al.	Chemotherapy-naive patients ES-SCLC ECOG PS 0-2 Excluded symptomatic CNS metastases or asymptomatic CNS metastases requiring concurrent corticosteroid therapy.	Pemetrexed 500 mg/m² plus carboplatin AUC 5 on day 1 Q3W - 6 cycles Etoposide 100 mg/m² on days 1-3 plus carboplatin AUC 5 Q3W - 6 cycles	1^0 - noninferiority of pemetrexed-carboplatin overall survival with a 15% margin As it has better side effect profile Terminated prematurely after 908 of 1,820 patients enrolled	Median OS – PC vs EC - 8.1 vs 10.6m HR 1.56 (p<0.001) Median PFS – 3.8 vs 5.4 months HR 1.85 (p<0.001) PC had higher grade 3-4 hematologic toxicities

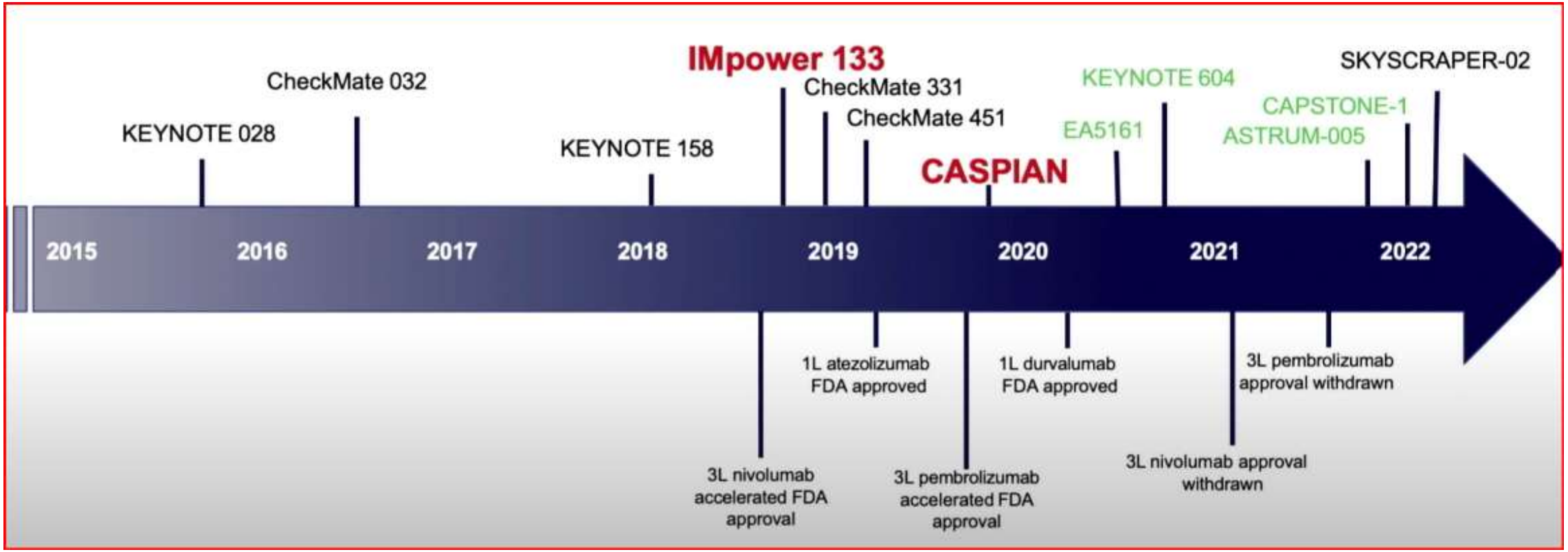
Socinski MA et al. J Clin Oncol. 2009 Oct 1;27(28):4787-92





Socinski MA et al. J Clin Oncol. 2009 Oct 1;27(28):4787-92

Checkpoint inhibitors and SCLC



Horn et al. IMPOWER 133	Confirmed ES SCLC ECOG PS 0/1 Treated asymptomatic brain metastasis were eligible n = 403	4# - 21 day Atezolizumab 1200 mg iv on day 1 + carboplatin AUC 5 D1 + Etoposide 100mg/m^2 D1-3 and Maintenance atezolizumab Placebo	Outcomes 1^o –OS, PFS 2^o- ORR, DOR, safety	Median OS – 12.3 vs 10.3 months HR – 0.76 (p=0.15) Median PFS – 5.3 vs 4.3 months

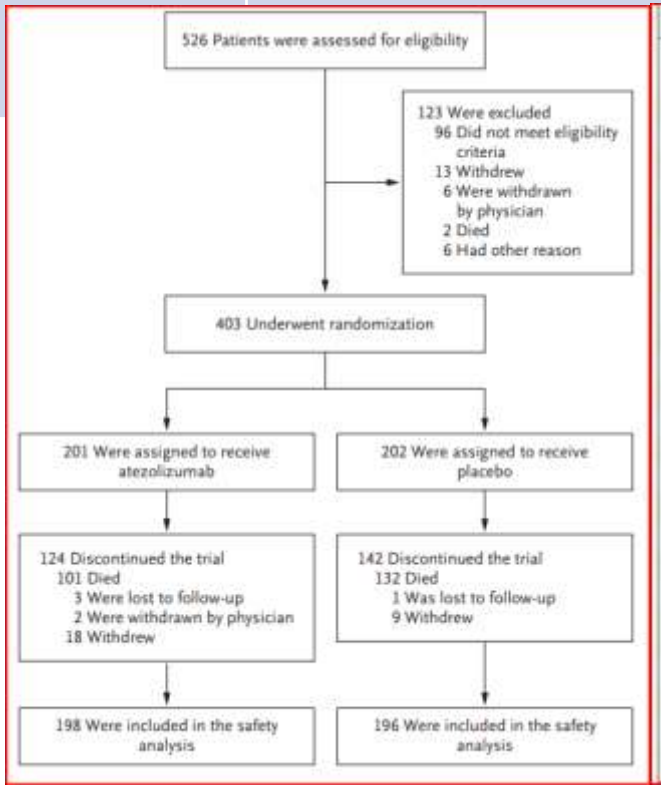
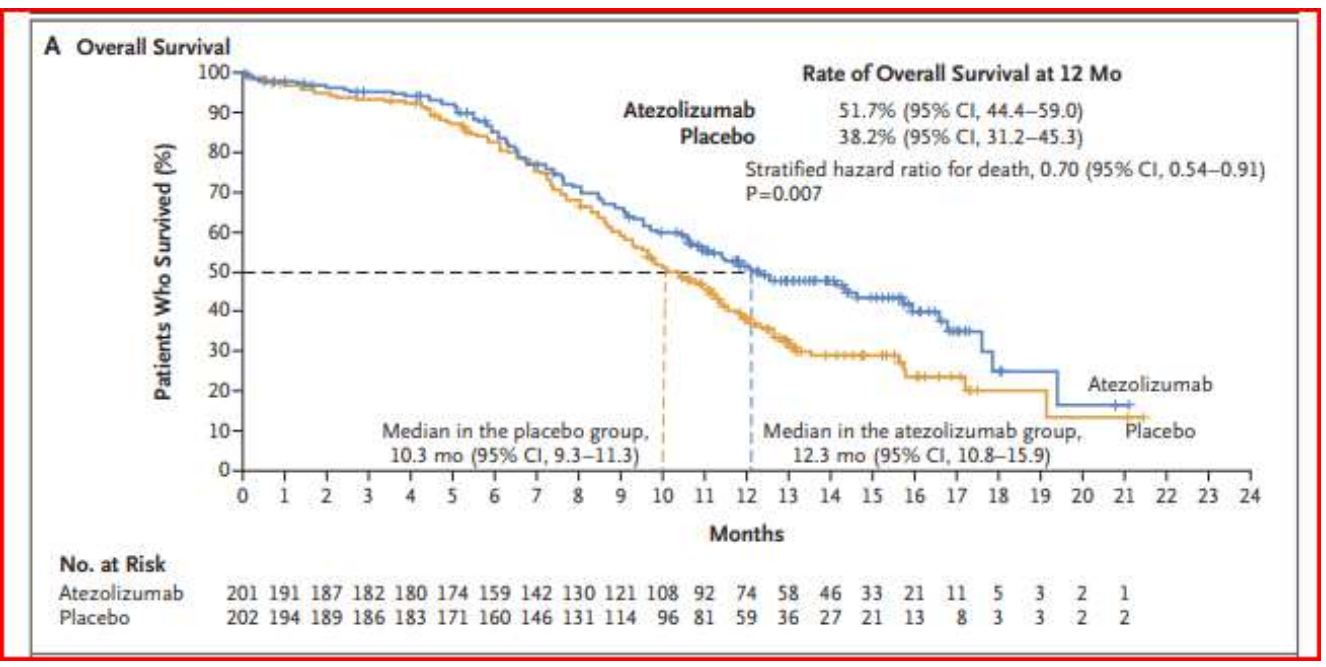


Table 1. Baseline Characteristics of All Enrolled Patients (Intention-to-Treat Population).

Characteristic	Atezolizumab Group (N = 201)	Placebo Group (N = 202)
Median age (range) — yr	64 (28–90)	64 (26–87)
Age group — no. (%)		
<65 yr	111 (55.2)	106 (52.5)
≥65 yr	90 (44.8)	96 (47.5)
Male sex — no. (%)†	129 (64.2)	132 (65.3)
ECOG performance-status score — no. (%)†‡		
0	73 (36.3)	67 (33.2)
1	128 (63.7)	135 (66.8)
Smoking status — no. (%)		
Never smoked	9 (4.5)	3 (1.5)
Current smoker	74 (36.8)	75 (37.1)
Former smoker	118 (58.7)	124 (61.4)
Brain metastasis at enrollment — no. (%)†	17 (8.5)	18 (8.9)
Blood-based tumor mutational burden — no./total no. (%)§		
<10 mutations/Mb	71/173 (41.0)	68/178 (38.2)
≥10 mutations/Mb	102/173 (59.0)	110/178 (61.8)
<16 mutations/Mb	133/173 (76.9)	138/178 (77.5)
≥16 mutations/Mb	40/173 (23.1)	40/178 (22.5)
Median sum of longest diameter of target lesions at baseline (range)	113.0 (12.0–325.0)	105.5 (15.0–353.0)
Previous anticancer treatments — no. (%)		
Chemotherapy or nonanthracycline¶	8 (4.0)	12 (5.9)
Radiotherapy	25 (12.4)	28 (13.9)
Cancer-related surgery	33 (16.4)	25 (12.4)

Leora Horn et al. N Engl J Med 2018;379:2220-2229


A Overall Survival
Rate of Overall Survival at 12 Mo
Atezolizumab 51.7% (95% CI, 44.4–59.0)
Placebo 38.2% (95% CI, 31.2–45.3)
Stratified hazard ratio for death, 0.70 (95% CI, 0.54–0.91)
P=0.007
Patients Who Survived (%)
Median in the placebo group, 10.3 mo (95% CI, 9.3–11.3)
Median in the atezolizumab group, 12.3 mo (95% CI, 10.8–15.9)
Atezolizumab
Placebo
Months
No. at Risk
Atezolizumab 201 191 187 182 180 174 159 142 130 121 108 92 74 58 46 33 21 11 5 3 2 1
Placebo 202 194 189 186 183 171 160 146 131 114 96 81 59 36 27 21 13 8 3 3 2 2

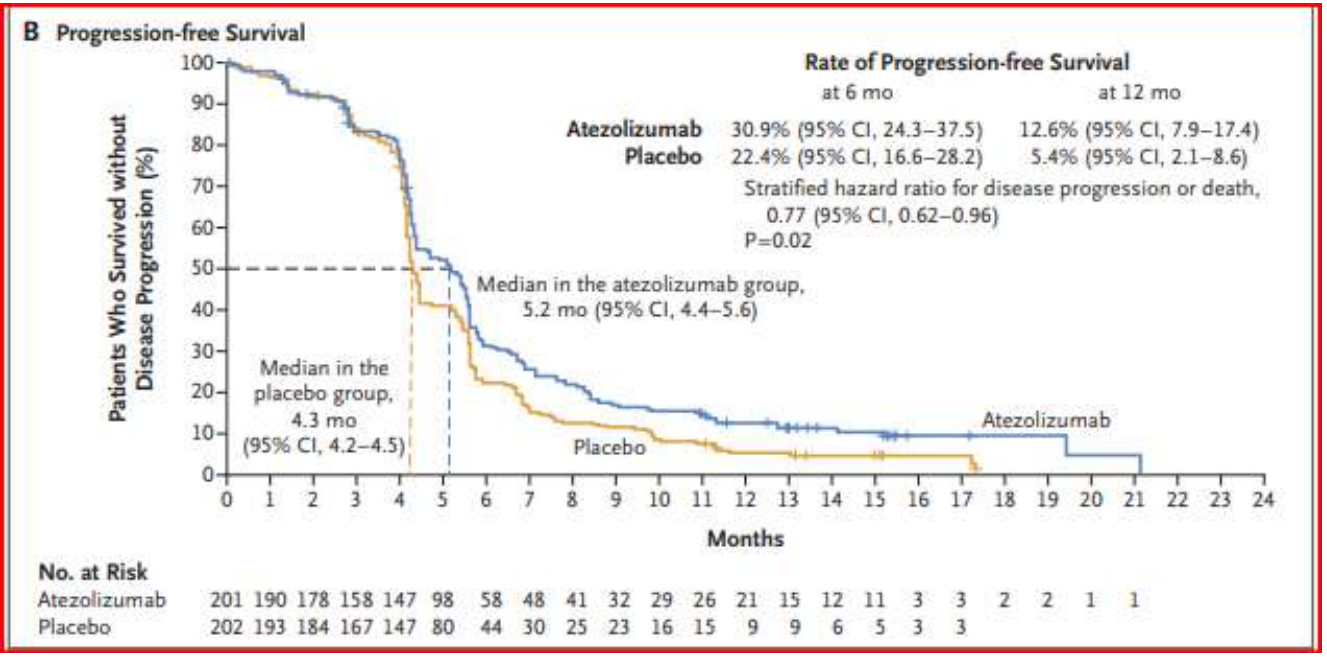

B Progression-free Survival
Rate of Progression-free Survival
at 6 mo at 12 mo
Atezolizumab 30.9% (95% CI, 24.3–37.5) 12.6% (95% CI, 7.9–17.4)
Placebo 22.4% (95% CI, 16.6–28.2) 5.4% (95% CI, 2.1–8.6)
Stratified hazard ratio for disease progression or death, 0.77 (95% CI, 0.62–0.96)
P=0.02
Patients Who Survived without Disease Progression (%)
Median in the atezolizumab group, 5.2 mo (95% CI, 4.4–5.6)
Median in the placebo group, 4.3 mo (95% CI, 4.2–4.5)
Atezolizumab
Placebo
Months
No. at Risk
Atezolizumab 201 190 178 158 147 98 58 48 41 32 29 26 21 15 12 11 3 3 2 2 1 1
Placebo 202 193 184 167 147 80 44 30 25 23 16 15 9 9 6 5 3 3

Table 2. Response Rate, Duration of Response, and Disease Progression.*

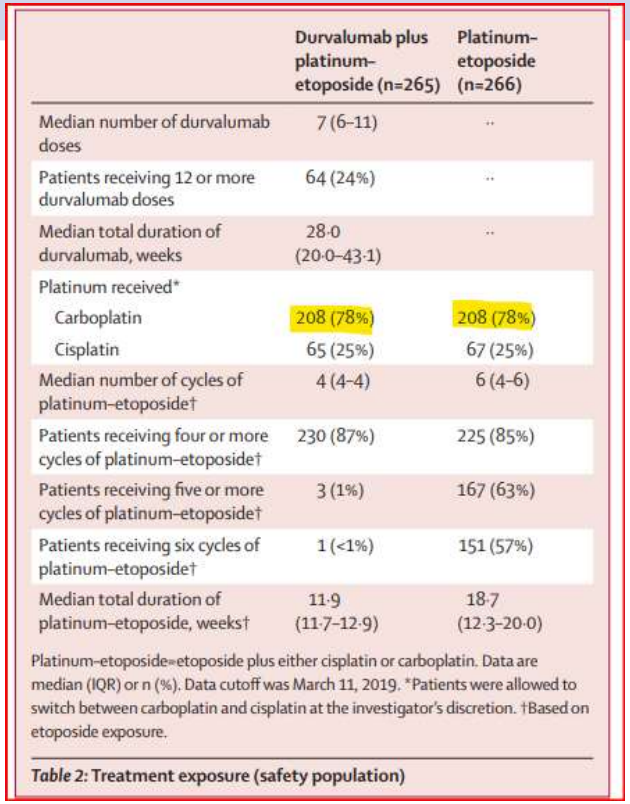
Variable	Atezolizumab Group (N=201)	Placebo Group (N=202)
Objective confirmed response†	121 (60.2 [53.1–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 (1.4§–19.5)	3.9 (2.0–16.1§)
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4])

Patients — no. (%)	Atezolizumab Group (N=198)	Placebo Group (N=196)
Rash		
All grades	37 (18.7)	20 (10.2)
Grade 3–4	4 (2.0)	0
Hypothyroidism		
All grades	25 (12.6)	1 (0.5)
Grade 3–4	0	0
Hepatitis (diagnosis)		
All grades	14 (7.1)	9 (4.6)
Grade 3–4	3 (1.5)	0
Hepatitis (laboratory abnormalities)		
All grades	14 (7.1)	9 (4.6)
Grade 3–4	3 (1.5)	0
Infusion-related reaction		
All grades	11 (5.6)	10 (5.1)
Grade 3–4	4 (2.0)	1 (0.5)
Hyperthyroidism		
All grades	11 (5.6)	5 (2.6)
Grade 3–4	0	0
Pneumonitis		
All grades	4 (2.0)	5 (2.6)
Grade 3–4	1 (0.5)	2 (1.0)
Colitis		
All grades	3 (1.5)	0
Grade 3–4	2 (1.0)	0

Table 3. Adverse Events Related to the Trial Regimen.*

Event	Atezolizumab Group (N=198)			Placebo Group (N=196)		
	Grade 1 or 2	Grade 3 or 4	Grade 5	Grade 1 or 2	Grade 3 or 4	Grade 5
	number of patients (percent)					
Any adverse event	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
Adverse events with an incidence of ≥10% in any grade category or events of grade 3 or 4 with an incidence of ≥2% in either group						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Alopecia	69 (34.8)	0	0	66 (33.7)	0	0
Nausea	62 (31.3)	1 (0.5)	0	58 (29.6)	1 (0.5)	0
Fatigue	39 (19.7)	3 (1.5)	0	37 (18.9)	1 (0.5)	0
Decreased neutrophil count	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Decreased appetite	39 (19.7)	2 (1.0)	0	26 (13.3)	0	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Decreased platelet count	17 (8.6)	7 (3.5)	0	21 (10.7)	7 (3.6)	0
Vomiting	25 (12.6)	2 (1.0)	0	19 (9.7)	3 (1.5)	0
Constipation	19 (9.6)	1 (0.5)	0	25 (12.8)	0	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Decreased white-cell count	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0
Infusion-related reaction	6 (3.0)	4 (2.0)	0	9 (4.6)	1 (0.5)	0

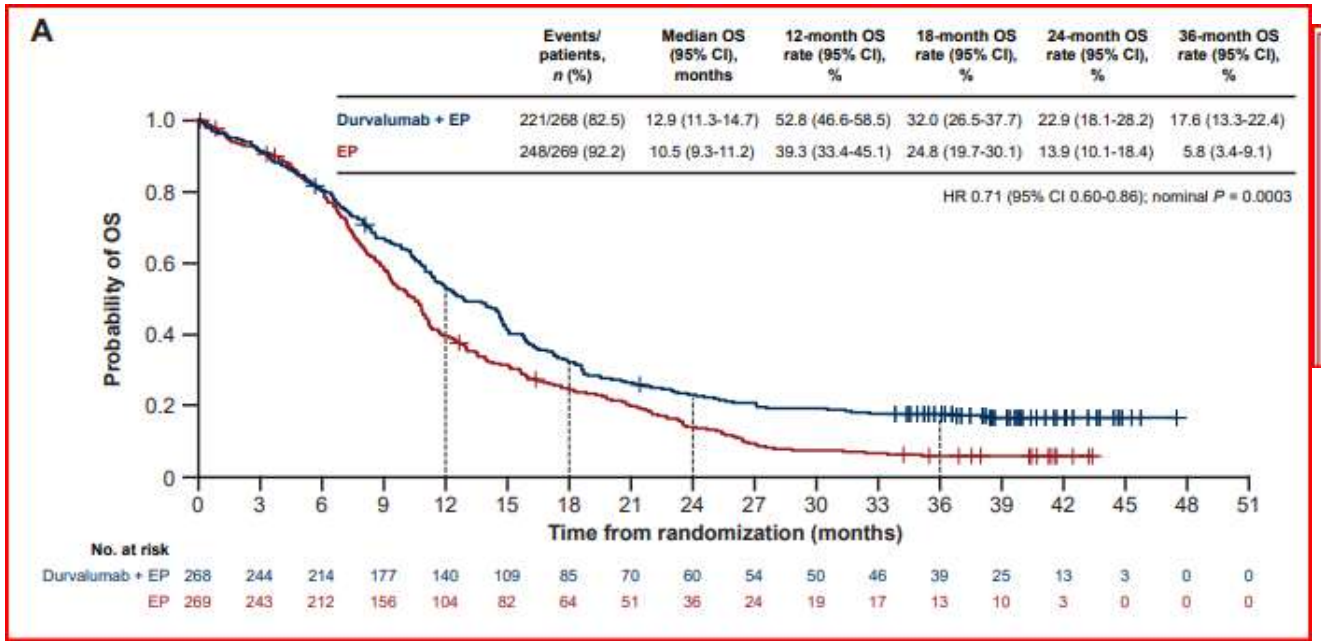
Luis Paz-Ares et al. CASPIAN March 17 - May 18	Confirmed ES SCLC With measurable ds. PS 0/1 Asymptomatic or treated and stable brain metastases permitted 12 wks or more life expectancy	Q 3W 4# OF A. durvalumab plus CT vs B. durvalumab +tremelimumab + CT, C. CT alone (Upto 6#) PCI +/- Maintenance – Durva Q4w in A and B	805 patients 268/268/269 Outcomes 1º –OS 2º – PFS, ORR, safety	Median OS – 12.9 vs 10.4 vs 10.5 months Median PFS – 45% vs 46% at 6m, 18% vs 5% at 12 m



	Durvalumab plus platinum–etoposide (n=265)	Platinum–etoposide (n=266)
Median number of durvalumab doses	7 (6–11)	..
Patients receiving 12 or more durvalumab doses	64 (24%)	..
Median total duration of durvalumab, weeks	28·0 (20·0–43·1)	..
Platinum received*		
Carboplatin	208 (78%)	208 (78%)
Cisplatin	65 (25%)	67 (25%)
Median number of cycles of platinum–etoposide†	4 (4–4)	6 (4–6)
Patients receiving four or more cycles of platinum–etoposide†	230 (87%)	225 (85%)
Patients receiving five or more cycles of platinum–etoposide†	3 (1%)	167 (63%)
Patients receiving six cycles of platinum–etoposide†	1 (<1%)	151 (57%)
Median total duration of platinum–etoposide, weeks†	11·9 (11·7–12·9)	18·7 (12·3–20·0)

Platinum–etoposide=etoposide plus either cisplatin or carboplatin. Data are median (IQR) or n (%). Data cutoff was March 11, 2019. *Patients were allowed to switch between carboplatin and cisplatin at the investigator's discretion. †Based on etoposide exposure.

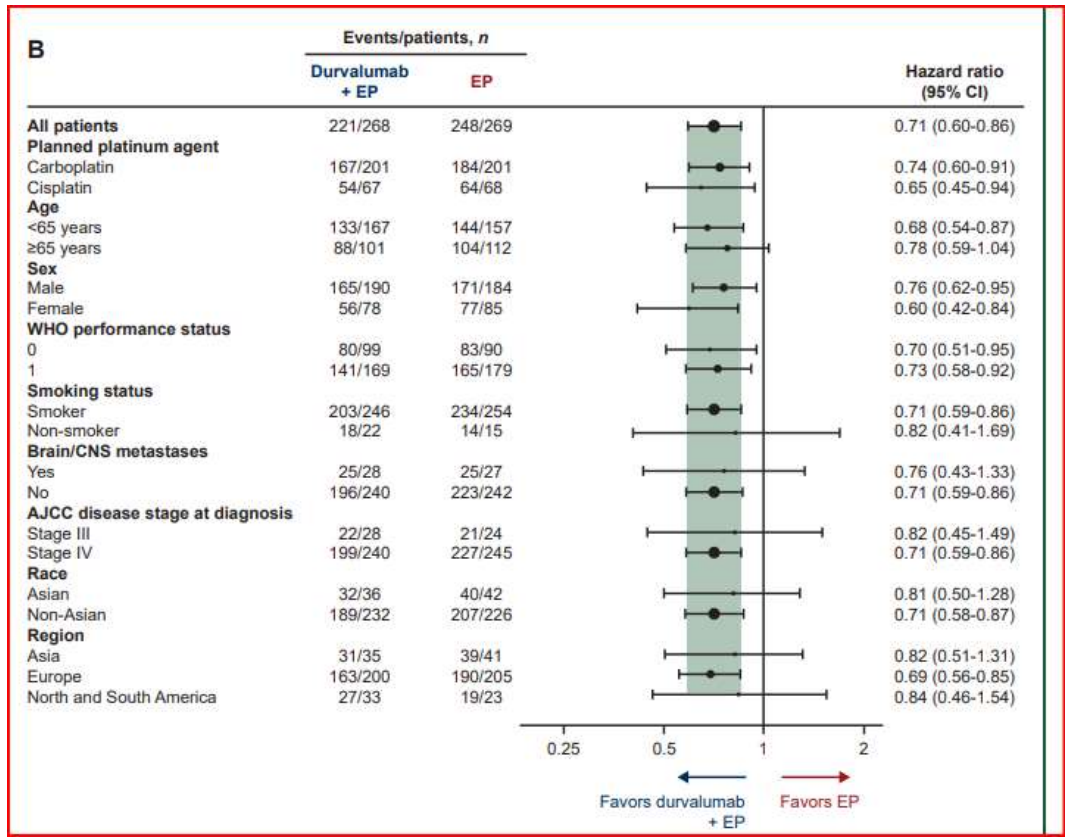
Table 2: **Treatment exposure (safety population)**



	Durvalumab plus platinum-etoposide (n=265)		Platinum-etoposide (n=266)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any event	260 (98%)	163 (62%)	258 (97%)	166 (62%)
Any serious event	82 (31%)	57 (22%)	96 (36%)	70 (26%)
Any event leading to discontinuation*	25 (9%)	7 (3%)	25 (9%)	7 (3%)
Any event leading to death†	13 (5%)	..	15 (6%)	..

Table 3. Response and progression-free survival in the 46 patients who remained on treatment with durvalumab at the 22 March 2021 data cut-off

	Durvalumab plus EP (n = 27)	Durvalumab plus tremelimumab plus EP (n = 19)
Best objective response[a]		
Responders, *n* (%)	23 (85.2)	19 (100.0)
Complete response[b]	6 (22.2)	4 (21.1)
Partial response[b]	17 (63.0)	15 (78.9)
Non-responders, *n* (%)	4 (14.8)	0
Stable disease ≥6 weeks	2 (7.4)	0
Progression	2 (7.4)	0
PFS[a]		
Progression events, *n* (%)	6 (22.2)	4 (21.1)
New lesions only	2 (7.4)	4 (21.1)
Target lesions only	4 (14.8)	0
PFS rate at 12 months, % (95% CI)[c]	85.2 (65.2-94.2)	84.2 (58.7-94.6)
PFS rate at 24 months, % (95% CI)[c]	81.5 (61.1-91.8)	78.9 (53.2-91.5)



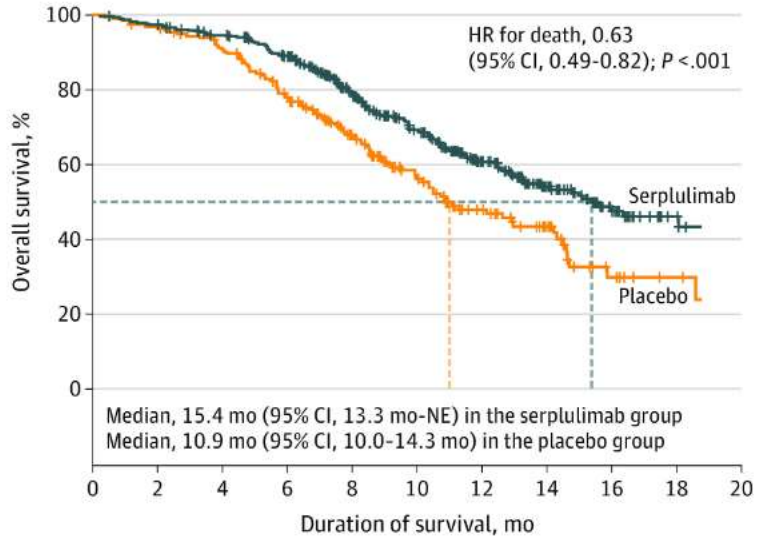
Paz-Ares, L. et al. ESMO Open, Volume 7, Issue 2, 100408

Rudin et al. (May 17 – July 18) KEYNOTE 604	Confirmed ES SCLC	Pembrolizumab + etoposide/carboplatin vs E/P	453 patients Outcomes 1^{o} – PFS, OS 2^{o} – ORR, Duration of response	12 m PFS – 13.6% (P) VS 3.1% (no) No significant OS difference 24 m OS – 22.5% vs 11.2 %

Cheng Y et al ASTRUM -005	Confirmed ES SCLC ECOG PS 0/1 Atleast one measurable lesion n = 585 patients	2:1 Q3W up to 4# Serplulimab (4.5 mg/kg D1) + Carbo AUC 5 D1 + Etopo 100 mg/m^2 D1-3 followed by Q3W serplulimab Vs placebo PCI	Outcomes 1^o –OS 2^o- PFS, ORR, DOR, safety	Median OS – 15.4 vs 10.9 months HR – 0.63 (p<0.001) Median PFS – 5.3 vs 4.3 months

Cheng Y et al. JAMA. 2022 Sep 27;328(12):1223-1232

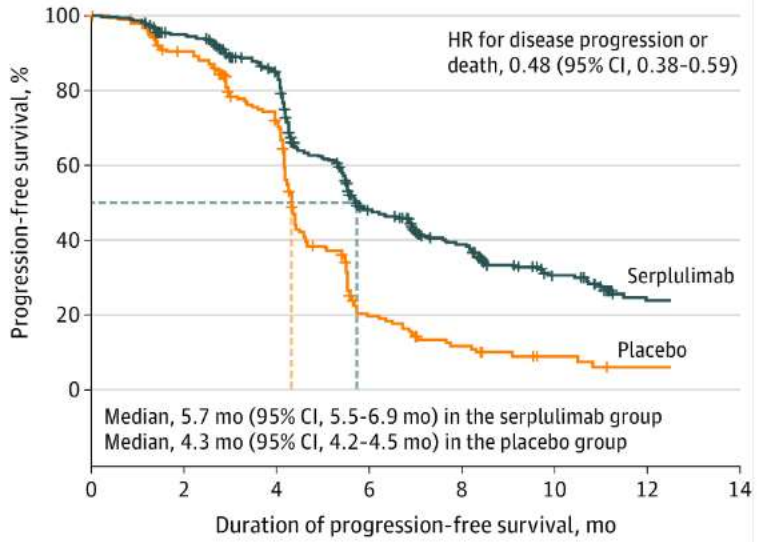
A Primary outcome of overall survival



No. at risk

Serplulimab	389	378	359	328	248	186	124	76	40	17
Placebo	196	189	174	144	106	72	48	29	11	6

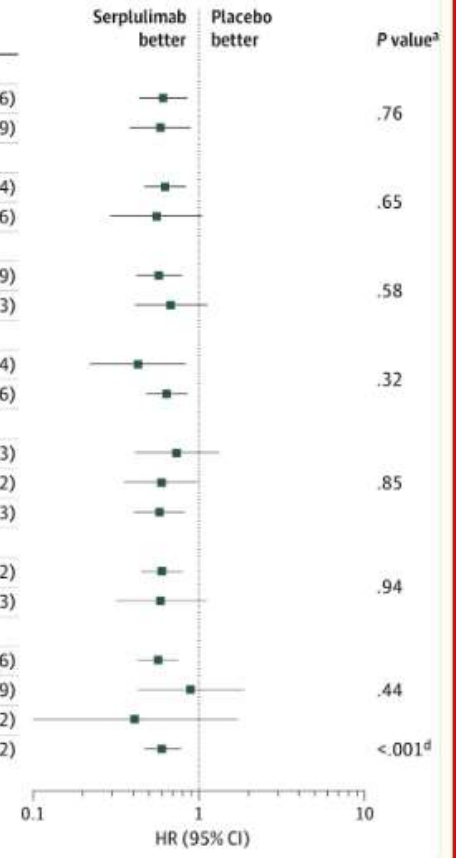
B Progression-free survival



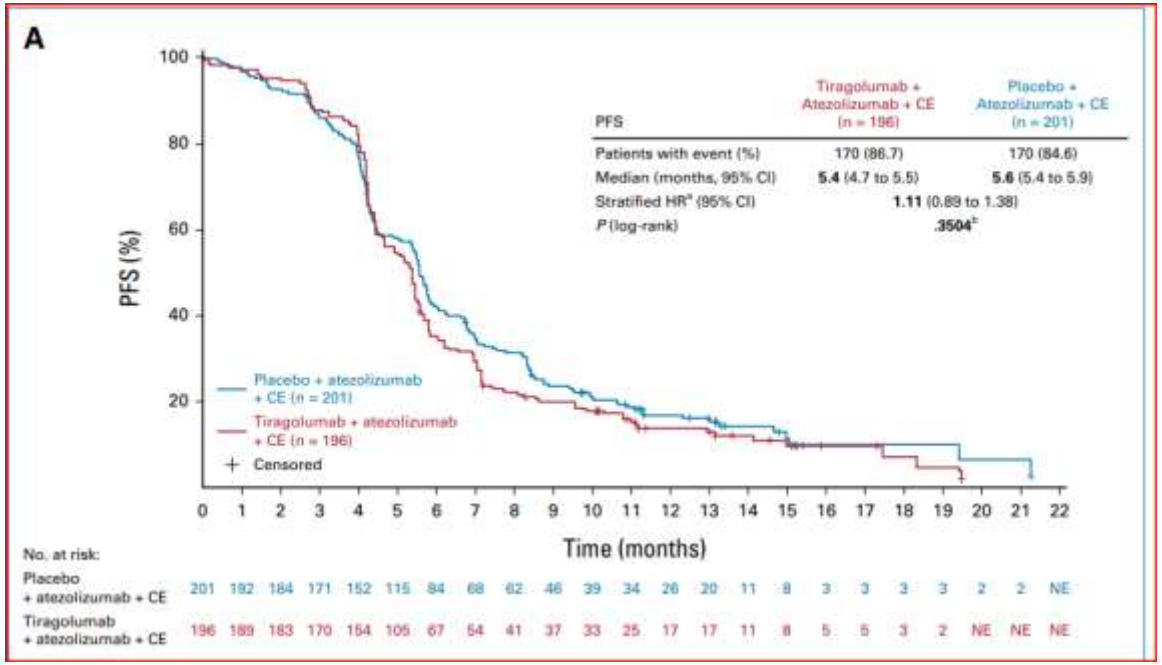
No. at risk

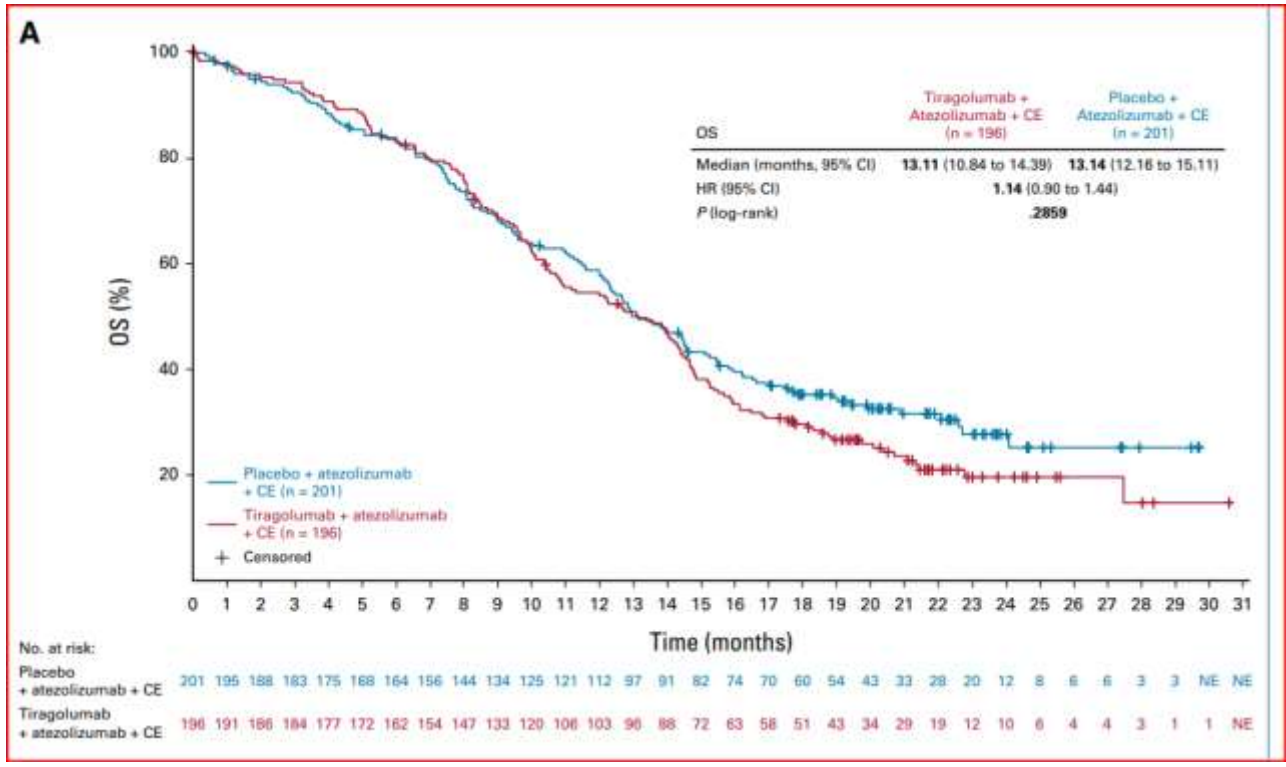
Serplulimab	389	337	280	131	87	55	26
Placebo	196	163	122	29	14	6	3

Subgroup	No. of patients		Median overall survival, mo		HR for death (95% CI)	P value[a]
	Serplulimab	Placebo	Serplulimab (n = 389)	Placebo (n = 196)		
Age, y						
<65	235	119	15.1	12.6	0.62 (0.45-0.86)	.76
≥65	154	77	15.4	10.0	0.60 (0.40-0.89)	
Sex						
Male	317	164	15.1	10.7	0.64 (0.48-0.84)	.65
Female	72	32	NR	14.2	0.57 (0.30-1.06)	
Race[b]						
Asian	262	139	16.0	11.1	0.58 (0.43-0.79)	.58
Non-Asian	127	57	12.6	10.5	0.70 (0.43-1.13)	
Baseline ECOG Performance Status Scale score[c]						
0	71	32	NR	11.1	0.44 (0.23-0.84)	.32
1	318	164	15.0	10.9	0.65 (0.49-0.86)	
Smoking history						
Never	81	35	15.0	14.2	0.75 (0.42-1.33)	.85
Current	102	48	16.0	12.2	0.61 (0.36-1.02)	
Former	206	113	15.4	10.5	0.59 (0.42-0.83)	
Brain metastases						
No	339	168	15.6	11.3	0.62 (0.47-0.82)	.94
Yes	50	28	13.9	10.0	0.61 (0.33-1.13)	
PD-L1 expression level						
Tumor proportion score <1%	317	152	15.0	10.5	0.58 (0.44-0.76)	.44
Tumor proportion score ≥1%	62	34	NR	12.9	0.92 (0.44-1.89)	
Not evaluable or not available	10	10	NR	14.2	0.42 (0.10-1.72)	
Overall	389	196	15.4	10.9	0.63 (0.49-0.82)	<.001[d]



Rudin CM et al. SKYSCRAPER 02	1L ES – SCLC with measurable disease Treated or untreated brain metastasis n = 490	4# - 21 day Tiragolumab iv Q3W + Atezolizumab 1200 mg Q3W + Carbo/etopo Maintenance – Tira + Atezo Placebo + Atezolizu + C/E Maintenance – Atezolizu	Outcomes 1º –OS 2º- PFS, ORR, DOR, safety	No benefit

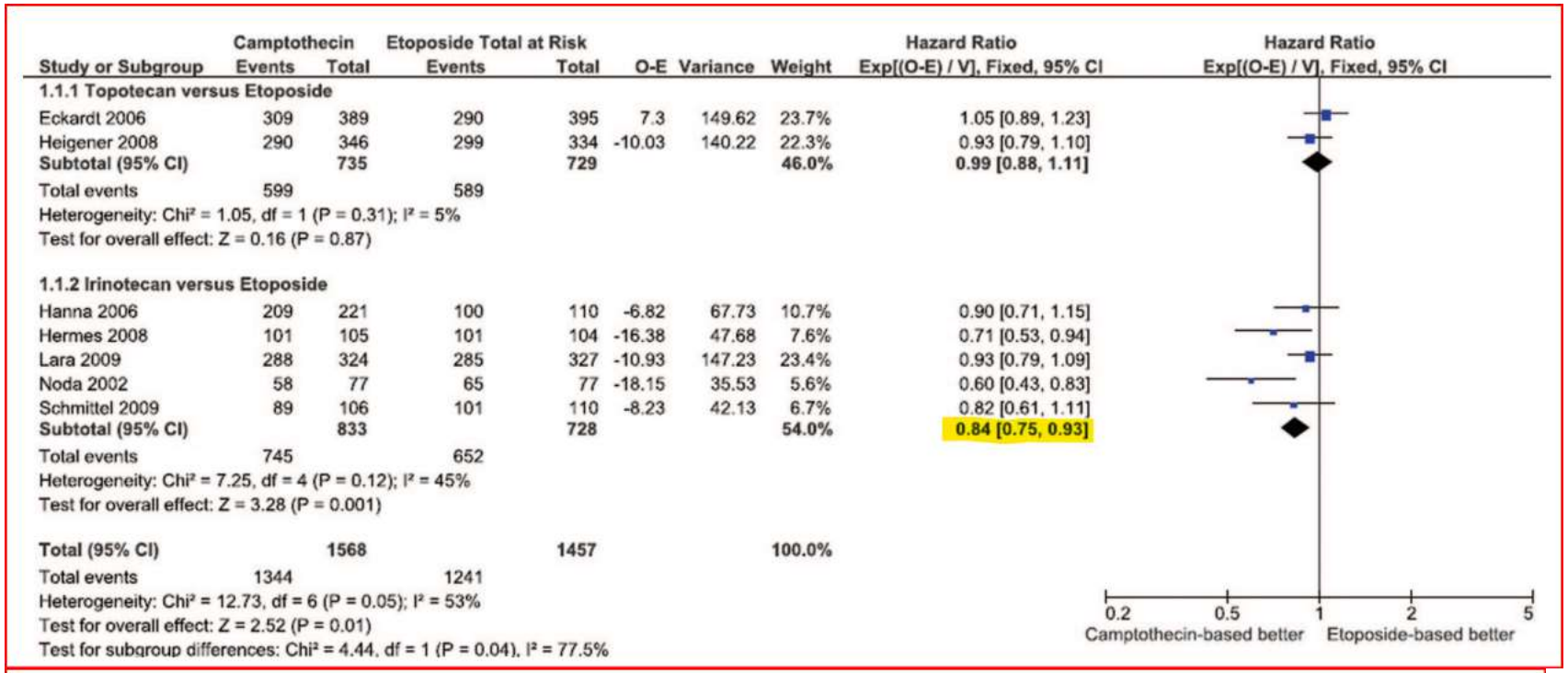

A
PFS (%)
Time (months)
Placebo + atezolizumab + CE (n = 201)
Tiragolumab + atezolizumab + CE (n = 196)
Censored
PFS
Tiragolumab + Atezolizumab + CE (n = 196)
Placebo + Atezolizumab + CE (n = 201)
Patients with event (%) 170 (86.7) 170 (84.6)
Median (months, 95% CI) 5.4 (4.7 to 5.5) 5.6 (5.4 to 5.9)
Stratified HR[a] (95% CI) 1.11 (0.89 to 1.38)
P (log-rank) .3504[b]
No. at risk:
Placebo + atezolizumab + CE 201 192 184 171 152 115 84 68 62 46 39 34 26 20 11 8 3 3 3 3 2 2 NE
Tiragolumab + atezolizumab + CE 196 189 183 170 154 105 67 54 41 37 33 25 17 17 11 8 5 5 3 2 NE NE NE


A
OS (%)
Time (months)
Placebo + atezolizumab + CE (n = 201)
Tiragolumab + atezolizumab + CE (n = 196)
Censored
OS
Tiragolumab + Atezolizumab + CE (n = 196)
Placebo + Atezolizumab + CE (n = 201)
Median (months, 95% CI) 13.11 (10.84 to 14.39) 13.14 (12.16 to 15.11)
HR (95% CI) 1.14 (0.90 to 1.44)
P (log-rank) .2859
No. at risk:
Placebo + atezolizumab + CE 201 195 188 183 175 168 164 156 144 134 125 121 112 97 91 82 74 70 60 54 43 33 28 20 12 8 6 6 3 3 NE NE
Tiragolumab + atezolizumab + CE 196 191 186 184 177 172 162 154 147 133 120 106 103 96 88 72 63 58 51 43 34 29 19 12 10 6 4 4 3 1 1 NE

Systemic therapy in ES – SCLC

- 4-6# of cytotoxic chemotherapy
- Carboplatin AUC 5 day 1 + etoposide 100 mg/m2 days 1, 2, 3 + atezolizumab 1200 mg day 1 Q3W X 4# followed by maintenance atezolizumab 1200 mg Q3W or 1680 mg Q4W
- Carboplatin AUC 5–6 day 1 + etoposide 80–100 mg/m2 days 1, 2, 3 + durvalumab 1500 mg Q3W x 4 # followed by maintenance durvalumab 1500 mg Q4W
- Cisplatin 75–80 mg/m2 day 1 + etoposide 80–100 mg/m2 days 1, 2, 3 + durvalumab 1500 mg Q3W X 4 # followed by maintenance durvalumab 1500 mg Q4W

Other systemic therapy options



Study or Subgroup	Camptothecin Events	Camptothecin Total	Etoposide Total at Risk Events	Etoposide Total at Risk Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Topotecan versus Etoposide								
Eckardt 2006	309	389	290	395	7.3	149.62	23.7%	1.05 [0.89, 1.23]
Heigener 2008	290	346	299	334	-10.03	140.22	22.3%	0.93 [0.79, 1.10]
Subtotal (95% CI)		735		729			46.0%	**0.99 [0.88, 1.11]**
Total events	599		589					
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%								
Test for overall effect: Z = 0.16 (P = 0.87)								
1.1.2 Irinotecan versus Etoposide								
Hanna 2006	209	221	100	110	-6.82	67.73	10.7%	0.90 [0.71, 1.15]
Hermes 2008	101	105	101	104	-16.38	47.68	7.6%	0.71 [0.53, 0.94]
Lara 2009	288	324	285	327	-10.93	147.23	23.4%	0.93 [0.79, 1.09]
Noda 2002	58	77	65	77	-18.15	35.53	5.6%	0.60 [0.43, 0.83]
Schmittel 2009	89	106	101	110	-8.23	42.13	6.7%	0.82 [0.61, 1.11]
Subtotal (95% CI)		833		728			54.0%	**0.84 [0.75, 0.93]**
Total events	745		652					
Heterogeneity: Chi² = 7.25, df = 4 (P = 0.12); I² = 45%								
Test for overall effect: Z = 3.28 (P = 0.001)								
Total (95% CI)		1568		1457			100.0%	
Total events	1344		1241					
Heterogeneity: Chi² = 12.73, df = 6 (P = 0.05); I² = 53%								
Test for overall effect: Z = 2.52 (P = 0.01)								
Test for subgroup differences: Chi² = 4.44, df = 1 (P = 0.04), I² = 77.5%								

Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI

0.2 0.5 1 2 5

Camptothecin-based better Etoposide-based better

Study or Subgroup	Irinotecan Events	Irinotecan Total	Etoposide Events	Etoposide Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Hanna 2006	106	221	48	110	24.2%	1.19 [0.75, 1.89]
Lara 2009	194	324	186	327	53.8%	1.13 [0.83, 1.55]
Pan 2006	20	30	14	31	3.3%	2.43 [0.86, 6.85]
Schmittel 2009	57	106	57	110	18.7%	1.08 [0.63, 1.85]
Total (95% CI)		681		578	100.0%	**1.18 [0.94, 1.48]**
Total events	377		305			
Heterogeneity: Chi² = 2.03, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						

Odds Ratio M-H, Fixed, 95% CI

0.2 0.5 1 2 5

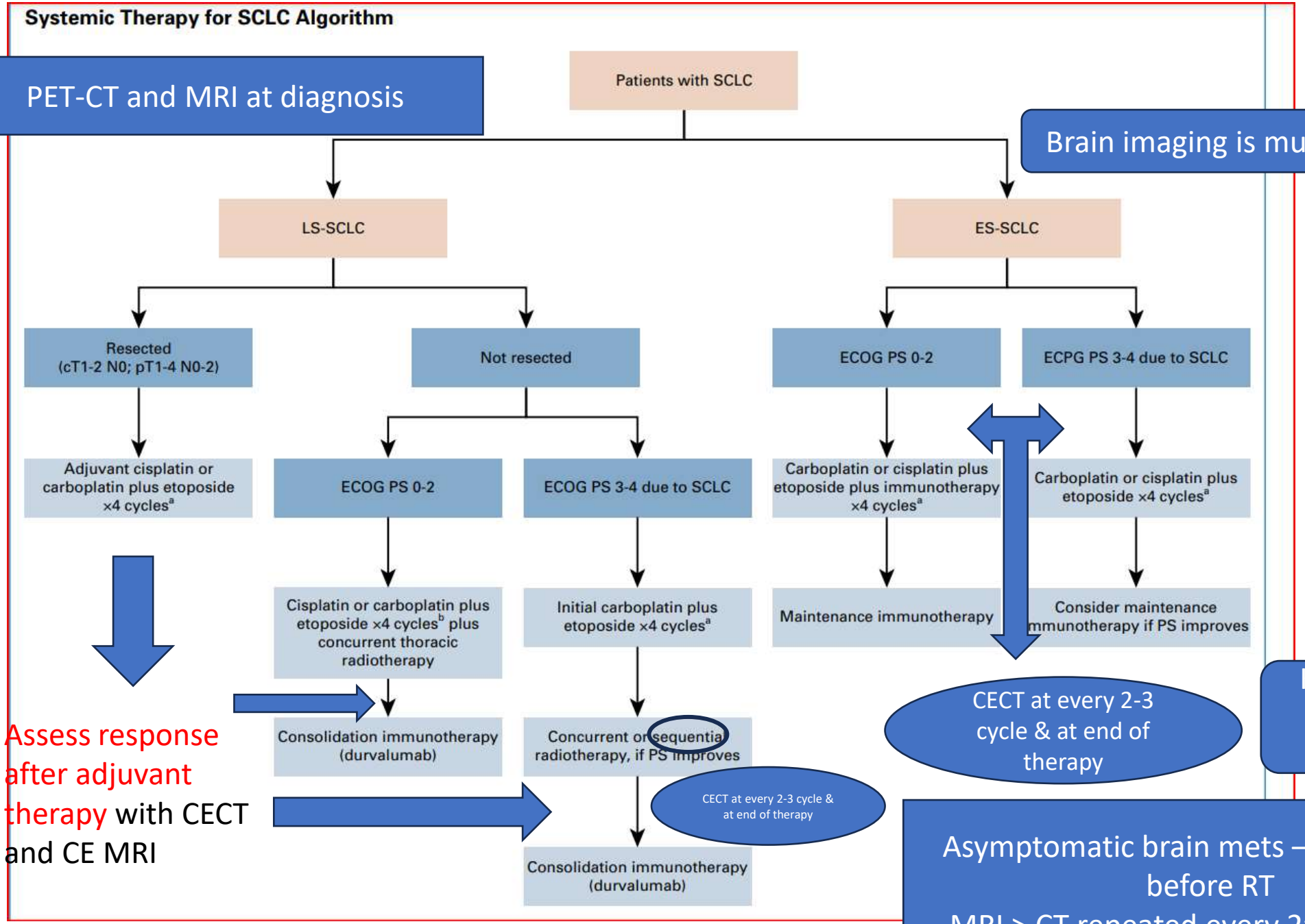
Etoposide-based better Irinotecan-based better

FIGURE 5. Overall response rate meta-analysis of irinotecan-based therapy trials.

TABLE 3. Grade 3 to Grade 4 Toxicities (CTC Scale) of Irinotecan-Based vs. Etoposide-Based Regimens

Grade 3 to Grade 4 Toxicities	No. of Patients	OR (95% CI)	*p*	I^2 (%)	NNH
Diarrhea	1598	8.94 (5.30–15.07)	<0.0001	40	7
Anemia	1598	0.52 (0.38–0.72)	0.0001	0	15
Leukopenia	1276	0.41 (0.32–0.53)	<0.00001	62	6
Neutropenia	1176	0.20 (0.16–0.27)	<0.00001	80	3
Neutropenic fever	538	0.43 (0.20–0.93)	0.03	0	26
Thrombocytopenia	1598	0.24 (0.17–0.34)	<0.00001	0	7

An OR <1 favors irinotecan-based therapy, whereas an OR >1 favors etoposide-based therapy.
OR, odds ratio; CI, confidence interval; NNH, number needed to harm; CTC, Common Toxicity Criteria.



PET-CT and MRI at diagnosis

Brain imaging is must

Assess response after adjuvant therapy with CECT and CE MRI

CECT at every 2-3 cycle & at end of therapy

Known brain mets – imaging every 3-4 months

Asymptomatic brain mets – receiving CT before RT
MRI > CT repeated every 2# and at end

RESPONSE ASSESSMENT

SURVEILLANCE FOR RELAPSE

- Chest CT (± abdomen/pelvis) is recommended every 2–6 months, more frequently in years 1–2, and less frequently thereafter [1]
- If new pulmonary nodule – evaluation for new primary lung cancer is necessary
- Brain MRI (preferred) or CT with contrast is advised every 3–4 months during year 1, then every 6 months as clinically indicated, regardless of PCI status – detect early metastasis
- FDG-PET/CT is not recommended for routine follow-up unless contrast CT is contraindicated

Manapov F et al. Tumori. 2013 Nov-Dec;99(6):656-60.

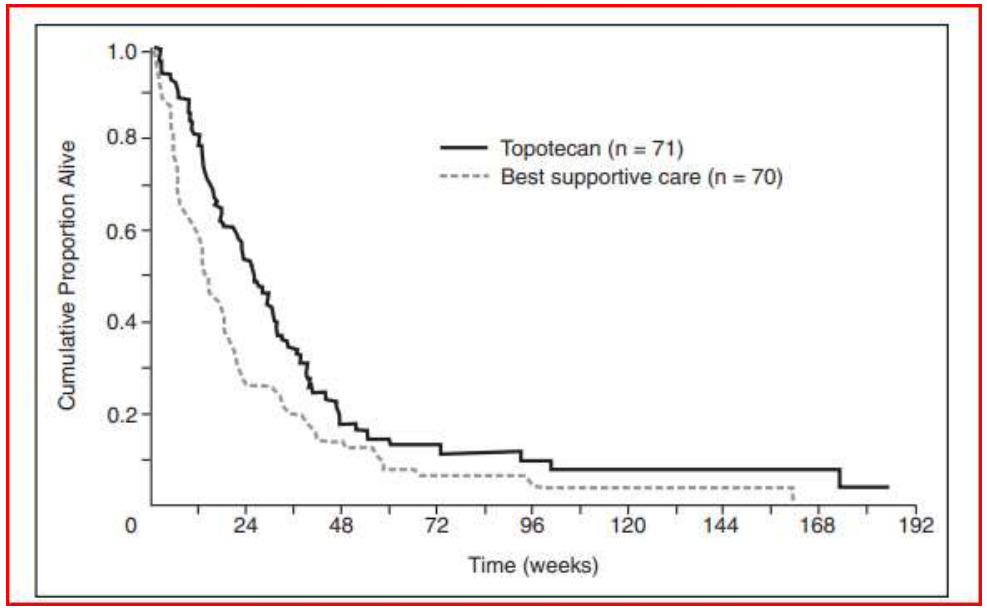
Management of relapse

- Depends on chemotherapy-free - free interval
  - 6 months or less - considered refractory or resistant
  - more than 6 months - considered sensitive disease
- ESMO guidelines considered 3 months as cut off rather than 6 months
- A meta analysis published in 2012 - 21 studies (1984–2011) = 1692 patients: 912 sensitive and 780 refractory
- Showed overall response rate with second line treatment is 17.9% (27.7 vs 14.8%) and pooled OR of response is 2.235 (1.518-3.291) favoring sensitive SCLC
- Median OS is 6.7 months (7.7 vs 5.4 months)

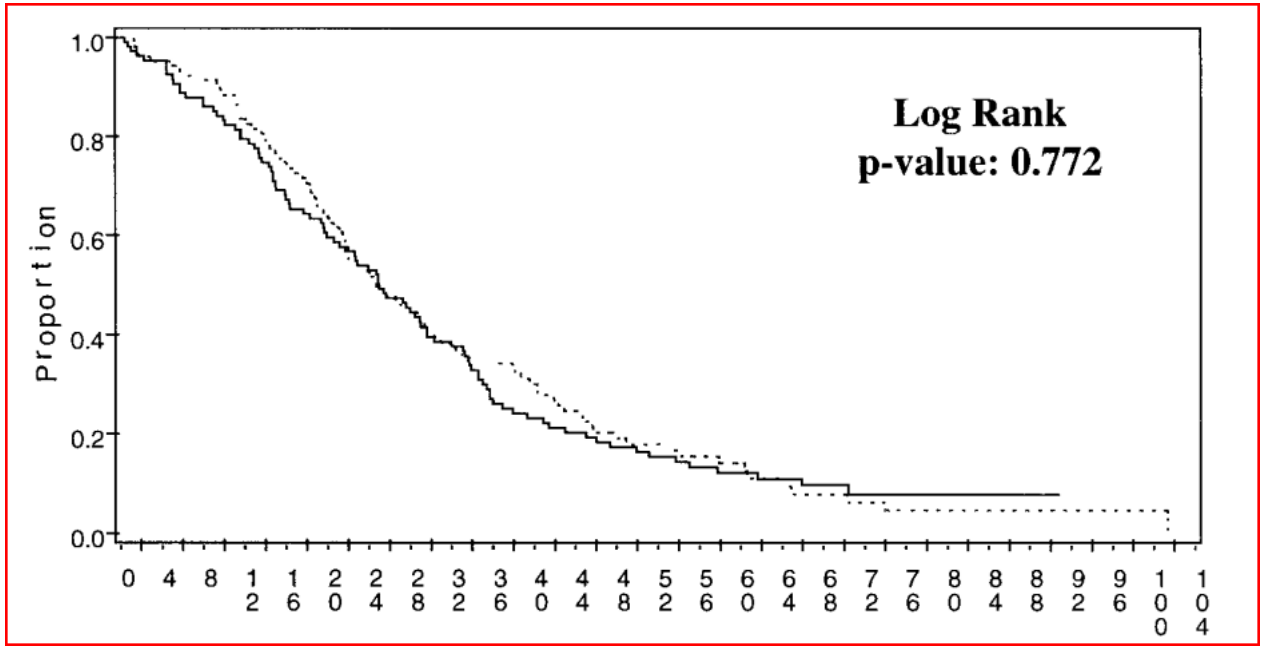
Owonikoko TK et al J Thorac Oncol. 2012 May;7(5):866-72.

Topotecan

A phase 3 study with relapsed SCLC after 45 days of first line showed oral topotecan improved median survival (25.9 weeks) compared to best supportive care (13.9 weeks)



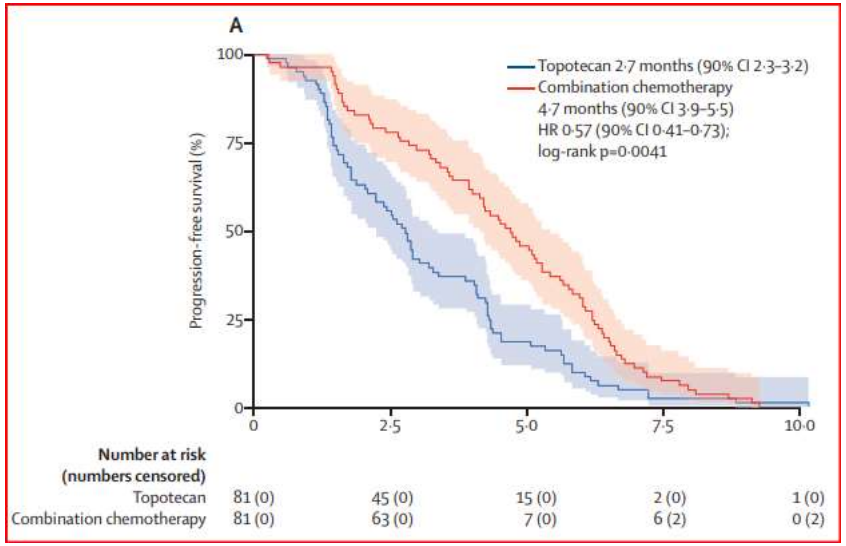
- A phase 3 study with relapsed SCLC (≥60 days after first-line treatment) compared iv topotecan vs cyclophosphamide, doxorubicin, and vincristine regimen
- Response rate: 24.3% vs 18.3%
- Median OS : 25.0 vs. 24.7 weeks
- Topotecan showed improved control of symptoms like dyspnea, anorexia, hoarseness, fatigue, and interference with daily activity (p≤0.043*p*≤0.043)

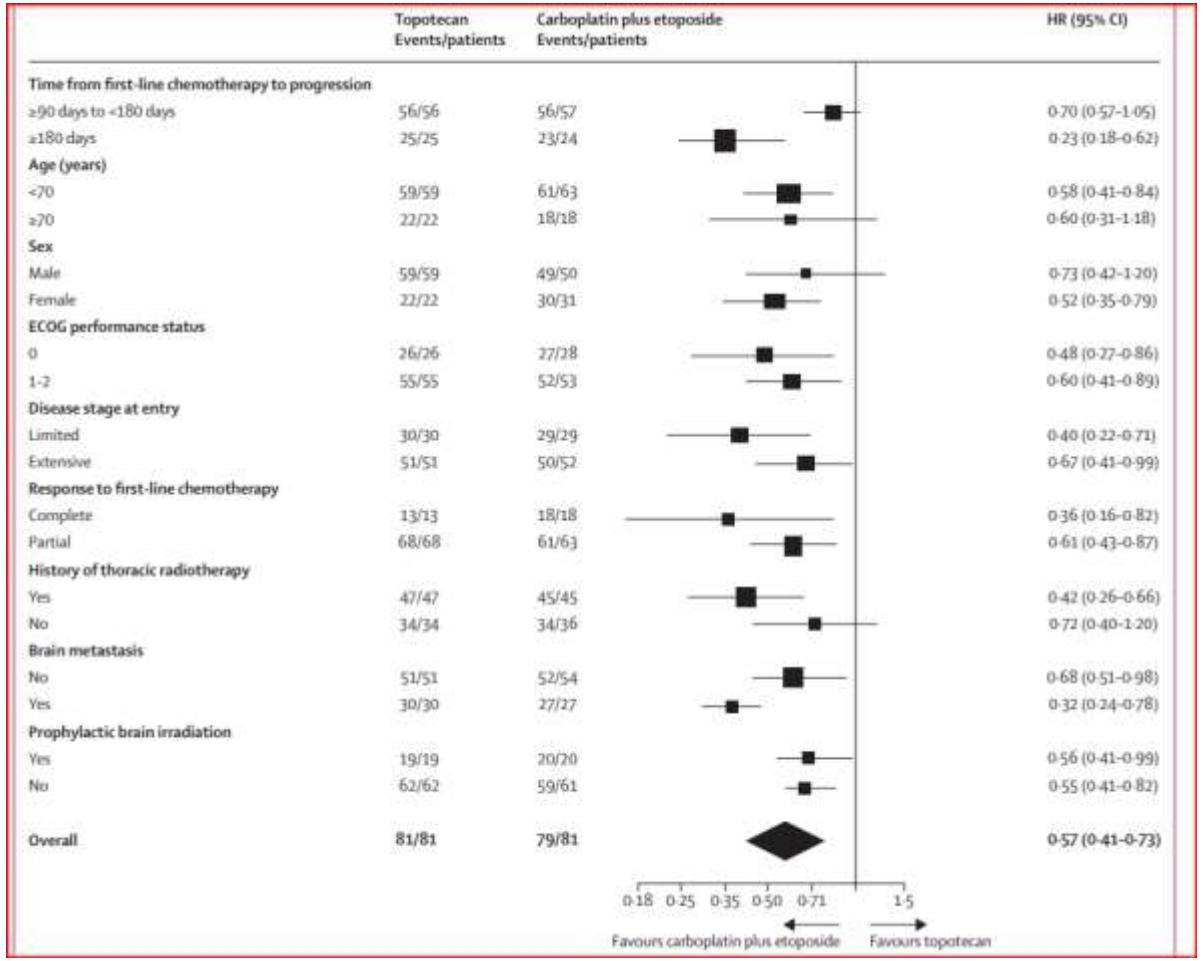


O'Brien ME et al. J Clin Oncol. 2006 Dec 1;24(34):5441-7
von Pawel J et al. J Clin Oncol. 1999 Feb;17(2):658-67

Platinum doublet rechallenge vs Topotecan

- Phase 3 RCT with relapsed SCLC with CTFI > 90 days and ECOG PS 0-2
- carboplatin plus etoposide (6# carboplatin AUC 5 D1 + etoposide [100 mg/m² D1-D3]) or oral topotecan (6# 2·3 mg/m² D1 - day 5)





Median follow-up: 22.7 months (IQR 20.0–37.3).
Median PFS - 4.7 months vs. 2.7 months stratified
HR: 0.57 (*p*=0.0041)

Grade 3–4 Adverse Events:

Neutropenia: 22% (topotecan) vs. 14% (combination).
Thrombocytopenia: 36% (topotecan) vs. 31% (combination).
Anemia: 21% (topotecan) vs. 25% (combination).
Febrile Neutropenia: 11% (topotecan) vs. 6% (combination).
Asthenia: 10% (topotecan) vs. 9% (combination).

LURBINECTEDIN

- Selective inhibitor of oncogenic transcription
- Binds to the minor groove of DNA, interfering with the transcription process and inducing double-strand DNA breaks -> apoptosis
- Modulates the tumor microenvironment by reducing the production of inflammatory cytokines and inhibiting macrophage recruitment

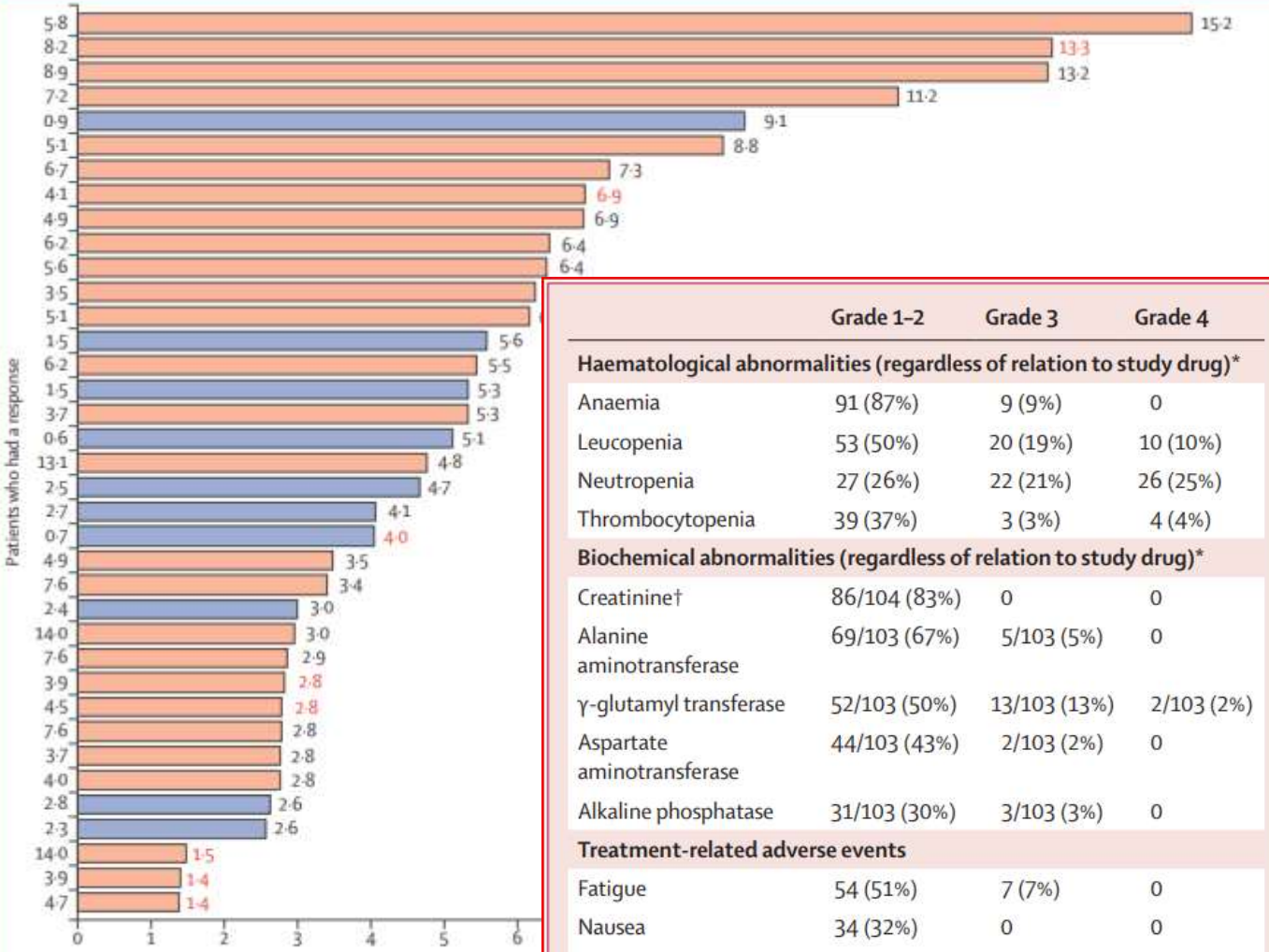
Trigo J et al. 2020 105 patients	Single arm Phase II study 26 hospitals in US/Europe Adult SCLC ECOG 0-2 Failed first line Measurable ds. No brain metastasis Adequate organ function	Lurbinectedin (3.2 mg/m^2) administered as a 1-hour IV infusion every 3 weeks until disease progression or unacceptable toxicity	1^0 – Overall response rate (CR/PR)	Median follow up – 17.1 Overall response rate – 35.2% Grade 3-4 ADR Neutropenia (46%) Leukopenia (29%)

Trigo J et al. Lancet Oncol. 2020 May;21(5):645-654.

	All patients (n=105)	Chemotherapy-free interval <90 days (n=45)	Chemotherapy-free interval ≥90 days (n=60)
RECIST responses			
Complete response	0	0	0
Partial response	37 (35%)	10 (22%)	27 (45%)
Stable disease*	35 (33%)	13 (29%)	22 (37%)
Progressive disease	28 (27%)	18 (40%)	10 (17%)
Not evaluable†	5 (5%)	4 (9%)	1 (2%)
Overall response, % (95% CI)	35·2% (26·2–45·2)	22·2% (11·2–37·1)	45·0% (32·1–58·4)
Disease control, % (95% CI)‡	68·6% (58·8–77·3)	51·1% (35·8–66·3)	81·7% (69·6–90·5)
Duration of response			
Disease progression, relapse, or death events in responding patients, n/N (%)	29/37 (78%)	9/10 (90%)	20/27 (74%)
Median duration of response, months	5·3 (4·1–6·4)	4·7 (2·6–5·6)	6·2 (3·5–7·3)
Patients still responding at 6 months	43·0% (25·6–60·5)	11·7% (0·0–33·1)	55·3% (34·5–76·0)
Progression-free survival			
Progression-free survival events, n (%)	90 (86%)	41 (91%)	49 (82%)
Median progression-free survival, months (95% CI)	3·5 (2·6–4·3)	2·6 (1·3–3·9)	4·6 (2·8–6·5)
4-month progression-free survival (95%CI)	46·6% (36·7–56·5)	29·1% (15·3–42·8)	59·9% (47·1–72·7)
6-month progression-free survival (95% CI)	32·9% (23·3–42·5)	18·8% (6·8–30·9)	43·5% (30·1–56·9)
Overall survival			
Deaths	66 (63%)	37 (82%)	29 (48%)
Median overall survival, months (95% CI)	9·3 (6·3–11·8)	5·0 (4·1–6·3)	11·9 (9·7–16·2)
6-month overall survival (95%CI)	67·1% (57·6–76·7)	45·8% (30·4–61·3)	83·6% (73·7–93·5)
12-month overall survival (95% CI)	34·2% (23·2–45·1)	15·9% (3·6–28·2)	48·3% (32·5–64·1)

RECIST=Response Evaluation Criteria in Solid Tumors. *Includes five patients with partial response not confirmed. †Five patients were not evaluable because they had no radiological assessment during treatment due to early death from malignant disease (n=2), symptomatic deterioration because of disease progression (n=2), and patient refusal (n=1). ‡Partial response or stable disease.

Table 2: Overall efficacy of lurbinectedin treatment by investigator assessment and subgroup analyses by chemotherapy-free interval



	Grade 1–2	Grade 3	Grade 4
Haematological abnormalities (regardless of relation to study drug)*			
Anaemia	91 (87%)	9 (9%)	0
Leucopenia	53 (50%)	20 (19%)	10 (10%)
Neutropenia	27 (26%)	22 (21%)	26 (25%)
Thrombocytopenia	39 (37%)	3 (3%)	4 (4%)
Biochemical abnormalities (regardless of relation to study drug)*			
Creatinine†	86/104 (83%)	0	0
Alanine aminotransferase	69/103 (67%)	5/103 (5%)	0
γ-glutamyl transferase	52/103 (50%)	13/103 (13%)	2/103 (2%)
Aspartate aminotransferase	44/103 (43%)	2/103 (2%)	0
Alkaline phosphatase	31/103 (30%)	3/103 (3%)	0
Treatment-related adverse events			
Fatigue	54 (51%)	7 (7%)	0
Nausea	34 (32%)	0	0
Decreased appetite	22 (21%)	0	0
Vomiting	19 (18%)	0	0
Diarrhoea	13 (14%)	1 (1%)	0
Febrile neutropenia	0	2 (2%)	3 (3%)
Pneumonia	0	2 (2%)	0
Skin ulcer	0	1 (1%)	0

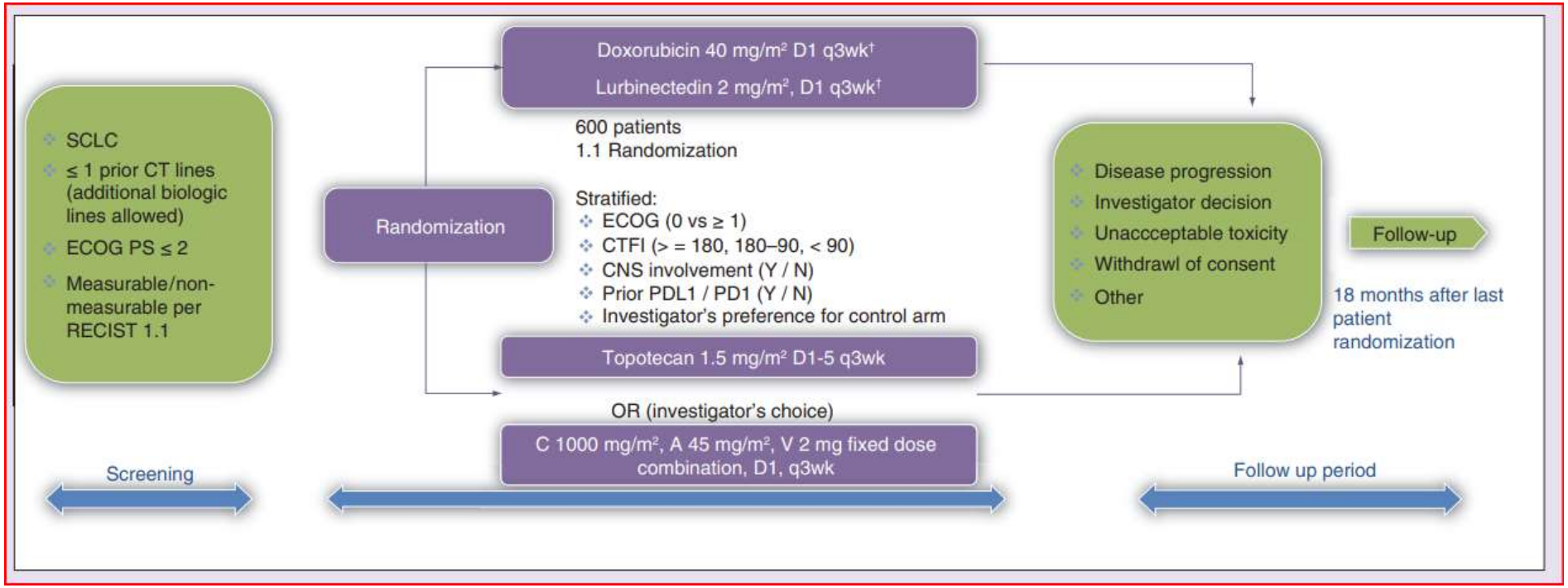
Trigo J et al. Lancet Oncol. 2020 May;21(5):645-654.

Augmenting DNA damage			
BAY 1895344 (ATR inhibitor)	1	Metastatic SCLC, neuroendocrine carcinoma, and pancreatic adenocarcinoma	NCT04514497
Iadademstat (KDM1A inhibitor; ORY-1001) or paclitaxel	2	SCLC or extrapulmonary G3 neuroendocrine carcinoma	NCT05420636
Lurbinectedin and berzosertib	1/2	SCLC and high-grade neuroendocrine cancers	NCT04802174
Lurbinectedin and sacituzumab govitecan	1/2	SCLC, extrapulmonary small-cell neuroendocrine cancer, and homologous recombination-deficient cancers resistant to PARP inhibitors	NCT04826341
Lurbinectidin in combination with atezolizumab compared with atezolizumab	3	SCLC after first-line carboplatin, etoposide, or atezolizumab	NCT05091567

Table 4
Main efficacy and safety outcomes in patients with sensitive SCLC (CTFI ≥ 90 and ≥180 days): platinum re-challenge and lurbinectedin.

	CTFI ≥ 90 days									CTFI ≥ 180 days	
	Platinum re-challenge								Lurbinectedin	Platinum re-challenge	Lurbinectedin
Reference	Korkmaz (2013) [5]	Inoue (2015) [6]	Wakuda (2015) [7]	Genestreti (2015) [8]	Shiozawa (2018) [9]	Naito (2018) [10]	Wakuda (2019) [11]	Monnet (2019) [12]	Trigo (2020) [19]	Wakuda (2015) [7]	Current analysis
STUDY DESIGN	Retrospective analysis	Phase II randomized	Retrospective analysis	Retrospective analysis	Retrospective analysis	Retrospective analysis	Retrospective analysis	Phase III randomized	Phase II single-arm	Retrospective analysis	Phase II single-arm
(n)	(n = 33)	(n = 30)	(n = 19)	(n = 112)	(n = 20)	(n = 67)	(n = 27)	(n = 81)	(n = 60)	(n = 11)	(n = 20)
Median CTFI (range)	NA	60 % CTFI >180 days	7.1 (3.1–39.2)	7.9 (3.0–39.5)	3.8 (3.0–13.2)	5.9 (3.1–50.0)	6.6 (3.1–38.7)	5.3 (4.7–5.8)	4.8 (3.0–16.1)	8.8 (6.0–38.7)	7.5 (6.0–16.1)
Age (years), median (range)	58 (NA)	67 (45–80)	69 (51–83)	64 (40–83)	65 (52–84)	NA	66 (51–73)	64 (NA)	59 (44–79)	69 (52–79)	57 (49–75)
Response first line %	NA	NA	95 %	98 %	NA	NA	98 %	NA	85 %	100 %	85 %
Limited disease, %	39 %	60 %	63 %	44 %	55 %	49 %	44 %	NA	42 %	73 %	65 %
ECOG PS 0–1, %	82 %	93 %	95 %	87 %	90 %	85 %	89 %	94 %	95 %	91 %	95 %
EFFICACY OUTCOMES											
ORR, %	55	43	37	45	50	52	48	49	45	46	60
(95 %CI)	(NA)	(28–58)	(19–59)	(NA)	(NA)	(NA)	(NA)	(NA)	(32–58)	(21–72)	(36–87)
Disease control rate, %	NA	80	84	64	80	82	74	86	82	73	95
(95 %CI)		(68–92)	(NA)	(NA)	(NA)	(NA)	(NA)	(NA)	(70–91)	(NA)	(75–100)
PFS (months), median	6.2	5.1	5.6	5.5	4.5	5.1	5.5	4.7	4·6	7.8	4.6
(95 %CI)	(NA)	(NA)	(NA)	(4.4–6.3)	(3.5–5.4)	(4.3–5.4)	(3.4–6.1)	(3.9–5.5)	(2.8–6.5)	(NA)	(2.6–7.3)
OS (months), median	11.4	14.3	14.4	7.9	10.5	10.8	14.2	7.5	11.9	15.7	16.2
(95 %CI)	(NA)	(NA)	(NA)	(6.9–9.7)	(7.9–13.0)	(8.7–14.5)	(6.4–25.6)	(5.4–9.5)	(9.7–16.2)	(NA)	(9.6-nr)
SAFETY OUTCOMES											
Primary G-CSF use	NA	No	NA	NA	NA	NA	NA	Yes	No	NA	No
Grade 3/4 neutropenia, %	NA	73 %	94 %	NA	65 %	NA	85 %	23 %	46 %	NA	45 %
Febrile neutropenia, %	NA	0%	16 %	NA	15 %	NA	19 %	6%	5%	NA	0%
Grade 3/4 thrombocytopenia, %	NA	27 %	26 %	NA	10 %	NA	37 %	41 %	7%	NA	10 %
Grade 3/4 fatigue, %	NA	3%	0%	NA	0%	NA	11 %	7%	7%	NA	10 %

Phase 3 ATLANTIS



Overall Survival:

- Median OS: 8.6 months vs. 7.6 months

- **Progressive disease was the most common reason for discontinuation** (70% in lurbinectedin + doxorubicin vs. 53% in control).

- Adverse Events:
  - Treatment-related deaths: <1% (lurbinectedin + doxorubicin) vs. 3% (control).
  - Grade 3+ hematological adverse events were less frequent in the lurbinectedin + doxorubicin group:
    - Anemia: 19% vs. 38%.
    - Neutropenia: 37% vs. 69%.
    - Thrombocytopenia: 14% vs. 31%.
  - Treatment discontinuation due to adverse events: 9% (lurbinectedin + doxorubicin) vs. 16% (control).

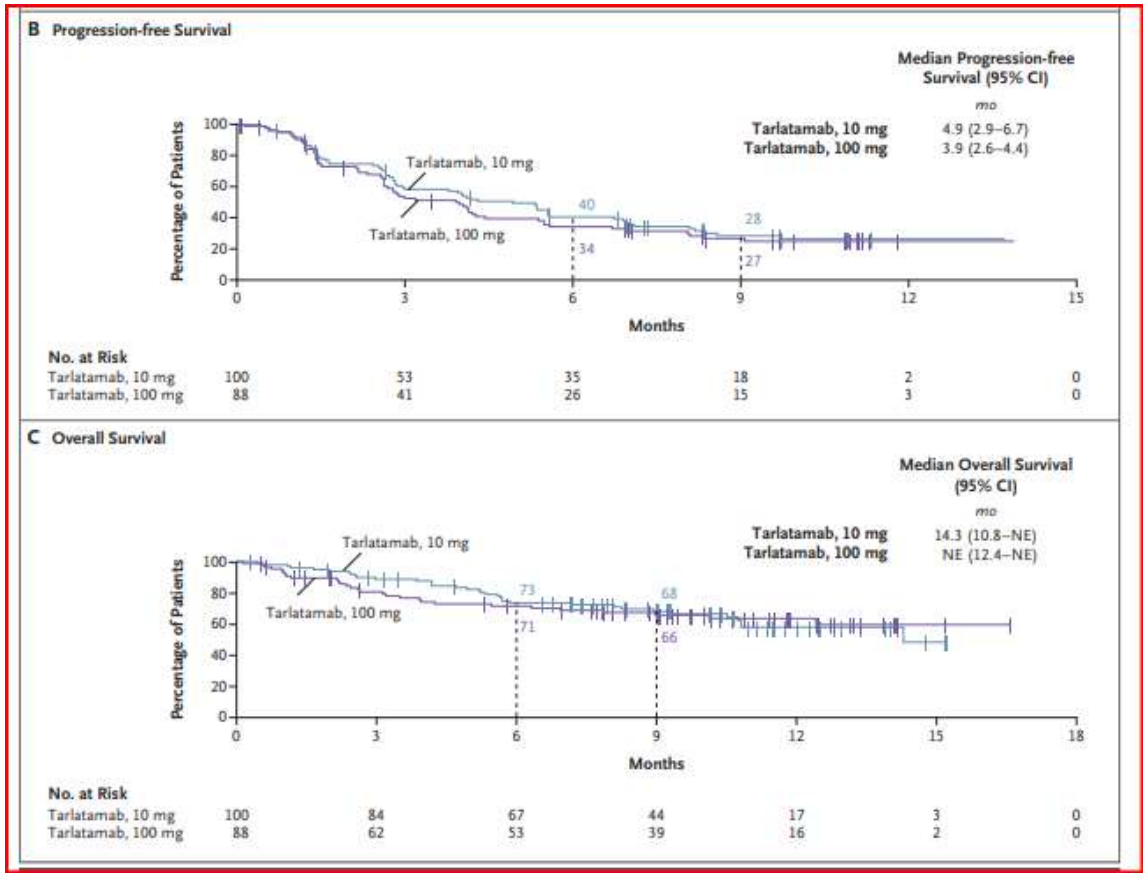
Tarlatamab - DeLLphi-301

- Bispecific T-cell engager (BiTE) immunotherapy that targets delta-like ligand 3 (DLL3), an antigen overexpressed in small-cell lung cancer (SCLC), and CD3 on T-cells -> facilitates T-cell activation and redirects cytotoxic T-cells to kill DLL3-expressing tumor cells

Ahn MJ et al. 2023 22- patients Median prior treatments are 2 EGOG PS 0/1	Single arm Phase II study	Iv Q2W at 10 mg or 100 mg	1^0 – Overall response rate (CR/PR)	**ORR – 40% vs 32%** **DOR** - ≥6 months in 59% of responders Ongoing responses in 55% (10-mg) and 57% (100-mg) Median PFS – 4.9 vs 3.9 9 months OS – 68% vs 66% Adv – cytokine release syndrome (51% vs 61%)

Table 2. Treatment Response According to Blinded Independent Central Review (Analysis Population for Antitumor Activity).*

Variable	Tarlatamab, 10 mg (N = 100)	Tarlatamab, 100 mg (N = 88)
Best overall response — no. (%)		
Objective response		
Confirmed complete response	1 (1)	7 (8)
Confirmed partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable†	2 (2)	4 (5)
Death before postbaseline scan†	6 (6)	13 (15)
No postbaseline scan†	2 (2)	3 (3)
Percentage of patients with objective response (97.5% CI)	40 (29–52)	32 (21–44)
Median duration of objective response (95% CI) — mo		
Overall	NE (5.9–NE)	NE (6.6–NE)
25th percentile	4.4 (2.8–7.1)	5.6 (2.8–7.6)
75th percentile	NE (NE–NE)	NE (NE–NE)
Observed duration of objective response — no./total no. (%)		
≥3 mo	35/40 (88)	25/28 (89)
≥6 mo	23/40 (58)	17/28 (61)
≥9 mo	10/40 (25)	10/28 (36)
Median time to objective response (range) — mo	1.4 (1.1–2.8)	1.4 (1.2–9.6)
Ongoing objective response at data cutoff — no./total no. (%)	22/40 (55)	16/28 (57)
Percentage of patients with disease control (95% CI)	70 (60–79)	63 (52–73)
Median duration of disease control (95% CI) — mo	6.9 (5.4–9.7)	6.7 (4.2–NE)

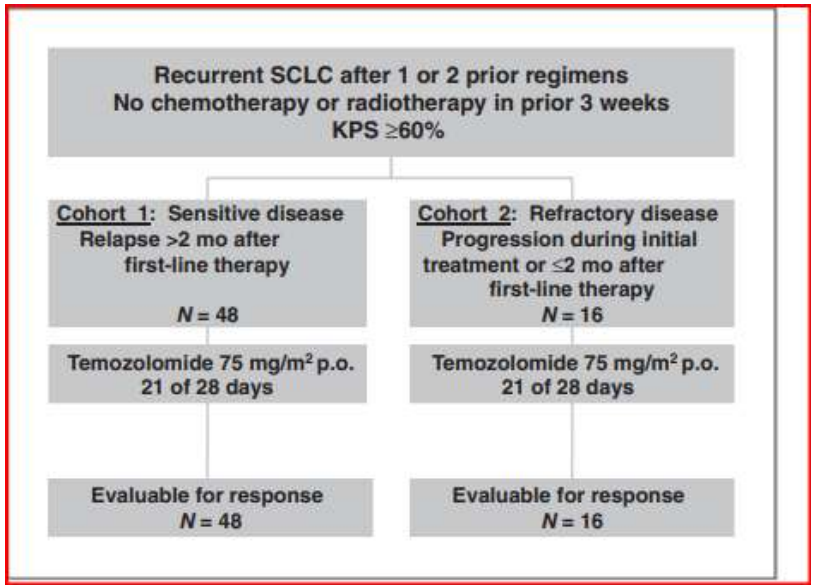


Events during treatment period			
According to severity			
Any grade	96 (97)	34 (100)	87 (100)
Grade ≥2	86 (87)	33 (97)	83 (95)
Grade ≥3	57 (58)	22 (65)	56 (64)
Grade ≥4	16 (16)	7 (21)	13 (15)
Fatal	3 (3)	4 (12)	5 (6)
Serious adverse event	58 (59)	14 (41)	62 (71)
Event leading to dose interruption, dose reduction, or both	31 (31)	5 (15)	39 (45)
Event leading to tarlatamab discontinuation	7 (7)	3 (9)	6 (7)
Events of interest during treatment period			
Cytokine-release syndrome†			
Overall	49 (49)	19 (56)	53 (61)
Grade ≥3 severity	0	1 (3)	5 (6)
Serious	26 (26)	5 (15)	32 (37)
Leading to tarlatamab discontinuation	0	0	1 (1)
Fatal	0	0	0
ICANS and associated neurologic events‡			
Overall	7 (7)	4 (12)	24 (28)
Grade ≥3 severity	0	0	4 (5)
Serious	2 (2)	2 (6)	11 (13)
Leading to tarlatamab discontinuation	1 (1)	0	1 (1)
Fatal	0	0	0
Neutropenia			
Overall	18 (18)	5 (15)	14 (16)
Grade ≥3 severity	6 (6)	2 (6)	9 (10)
Serious	2 (2)	0	3 (3)
Leading to tarlatamab discontinuation	0	0	0
Fatal	0	0	0

Targeting DLL3			
BI 764532 (DLL3–CD3 T-cell engaging bispecific antibody)	1	SCLC, LCNEC, neuroendocrine carcinoma, or small cell carcinoma of any other origin	NCT04429087
HPN328 (DLL3–CD3 trispecific T-cell activating construct)	1/2	SCLC, neuroendocrine prostate cancer, and high-grade NETs	NCT04471727
PT217 (CD47–DLL3 bispecific T-cell engager)	1	SCLC, LCNEC, neuroendocrine prostate cancer, and gastroenteropancreatic NETs	NCT05652686
RO7616789 (DLL3–CD3–CD137 trispecific T-cell engager)	1	SCLC and neuroendocrine carcinoma	NCT05619744
BI764532 (DLL3–CD3 bispecific antibody) in combination with enzabenlimab (anti-PD-1 antibody)	1	SCLC, LCNEC, and neuroendocrine carcinomas or small-cell tumours of any origin	NCT05879978
LB2102 (DLL3-directed chimeric antigen receptor T cells)	1	SCLC and LCNEC	NCT05680922

Temozolomide

- An oral alkylating agent that undergoes spontaneous hydrolysis at physiological pH to form the active compound, methyl-triazeno-imidazole-carboxamide (MTIC)
- MTIC methylates DNA at the O6 and N7 positions of guanine, leading to DNA damage, disruption of replication, and apoptosis in cancer cell



Pientanza et al 2012 64 patients 48 – sensitive 16 – Refractory	Single arm Phase II study	Temozolomide (75 mg/m2 /d) orally on days 1 to 21 of a 28-day cycle Tested for MGMT methylation	1^0 – Overall response rate (CR/PR)	Sensitive – 1 CR and 10 PR ORR = 23% Refractory – 2 PRs ORR = 13% 2^{nd} line treatment ORR: 22% 3^{rd} -line treatment ORR: 19% **Brain metastases: 38% CR or PR** **Numerically higher benefit in methylation positive patients**

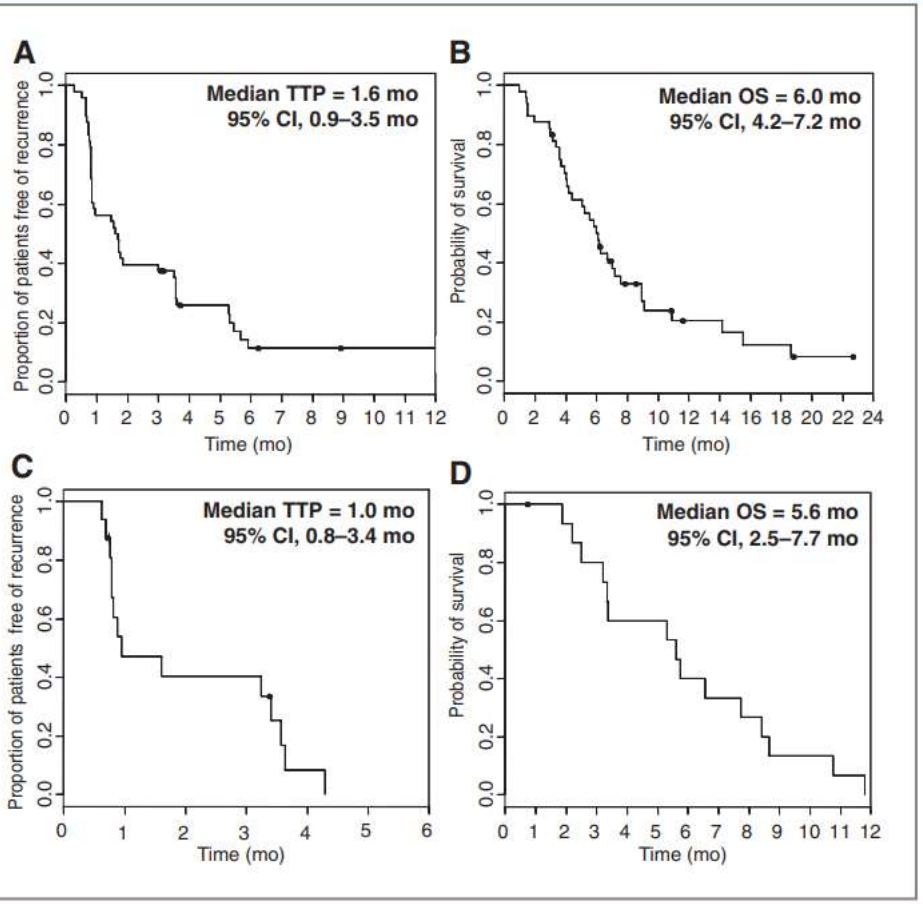


Figure 3. Kaplan–Meier curves for outcomes. A, TTP and B, OS for the 48 patients with platinum-sensitive SCLC. C, TTP and D, OS for the 16 patients with platinum-refractory SCLC.

Table 2. Adverse events

	Number of patients ($N = 64$)			
Toxicity	**Grade 1, *n* (%)**	**Grade 2, *n* (%)**	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**
Hematologic				
Anemia	6 (9)	9 (14)	2 (3)	
Thrombocytopenia	5 (8)	2 (3)	5 (8)	1 (2)
Leukopenia	6 (9)	2 (3)	1 (2)	1 (2)
Lymphopenia			17 (27)	2 (3)
Neutropenia		1 (2)	2 (3)	1 (2)
Febrile neutropenia			1 (2)	
MDS[a]				2 (3)
Nonhematologic				
Fatigue	18 (28)	23 (36)	2 (3)	
Nausea	22 (34)	9 (14)		
Vomiting	17 (27)	4 (6)		
Constipation	14 (22)	4 (6)		
Diarrhea	6 (9)	1 (2)		
Anorexia	5 (8)	2 (3)		
Rash/desquamation	4 (6)	1 (2)	2 (3)	
Transaminitis	4 (6)	2 (3)		

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[g]
Consider dose reduction or growth factor support for patients with PS 2

CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS

Preferred Regimens

- Clinical trial enrollment
- Re-treatment with platinum-based doublet[h,15-19]

Other Recommended Regimens

- Lurbinectedin[20,21]
- Topotecan oral (PO) or intravenous (IV)[22-25]
- Irinotecan[i,25,26]
- Tarlatamab-dlle[j,28]

CTFI ≤6 MONTHS

Preferred Regimens

- Clinical trial enrollment
- Lurbinectedin[20,21]
- Topotecan oral (PO) or intravenous (IV)[17,22-25]
- Irinotecan[i,25,26]
- Tarlatamab-dlle[j,28]
- Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[h,17-19]

Other Recommended Regimens

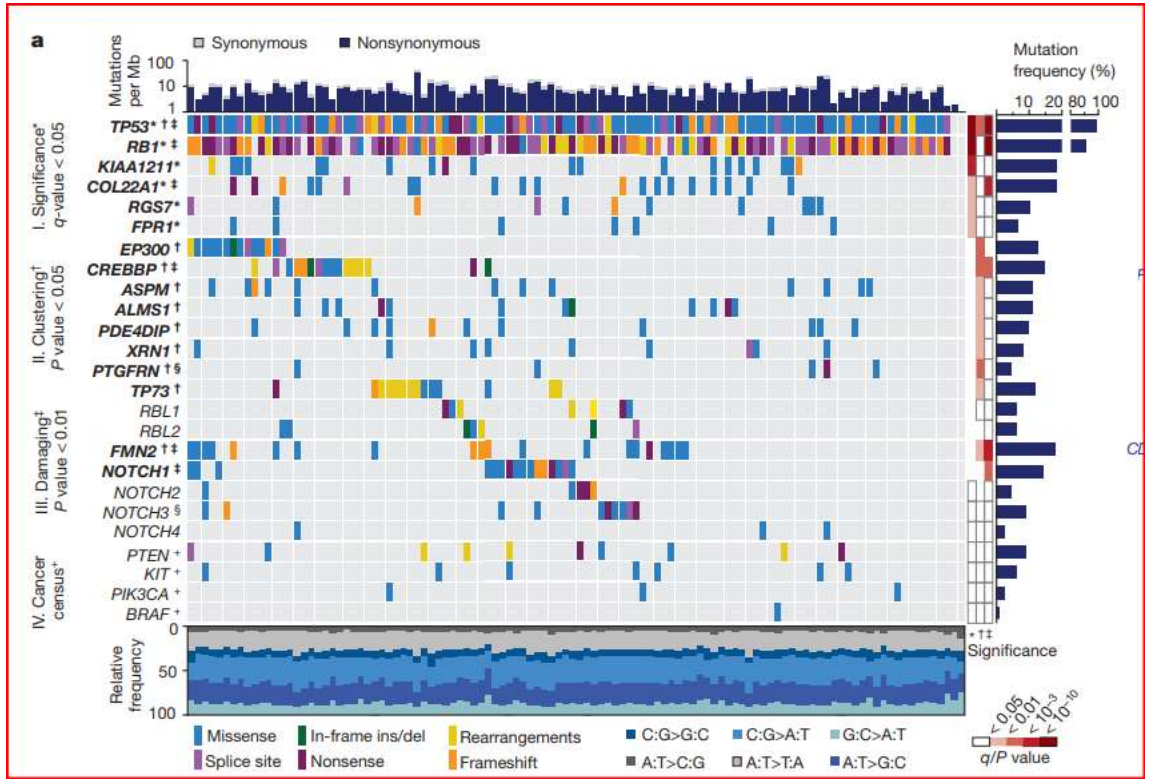
- Nivolumab or pembrolizumab (if not previously treated with an ICI)[d,29-33]
- Paclitaxel[34,35]
- Temozolomide[36,37]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[22]
- Docetaxel[38]
- Gemcitabine[27,39,40]
- Oral etoposide[41,42]

What predicts response to treatment in few?

Characters of SCLC

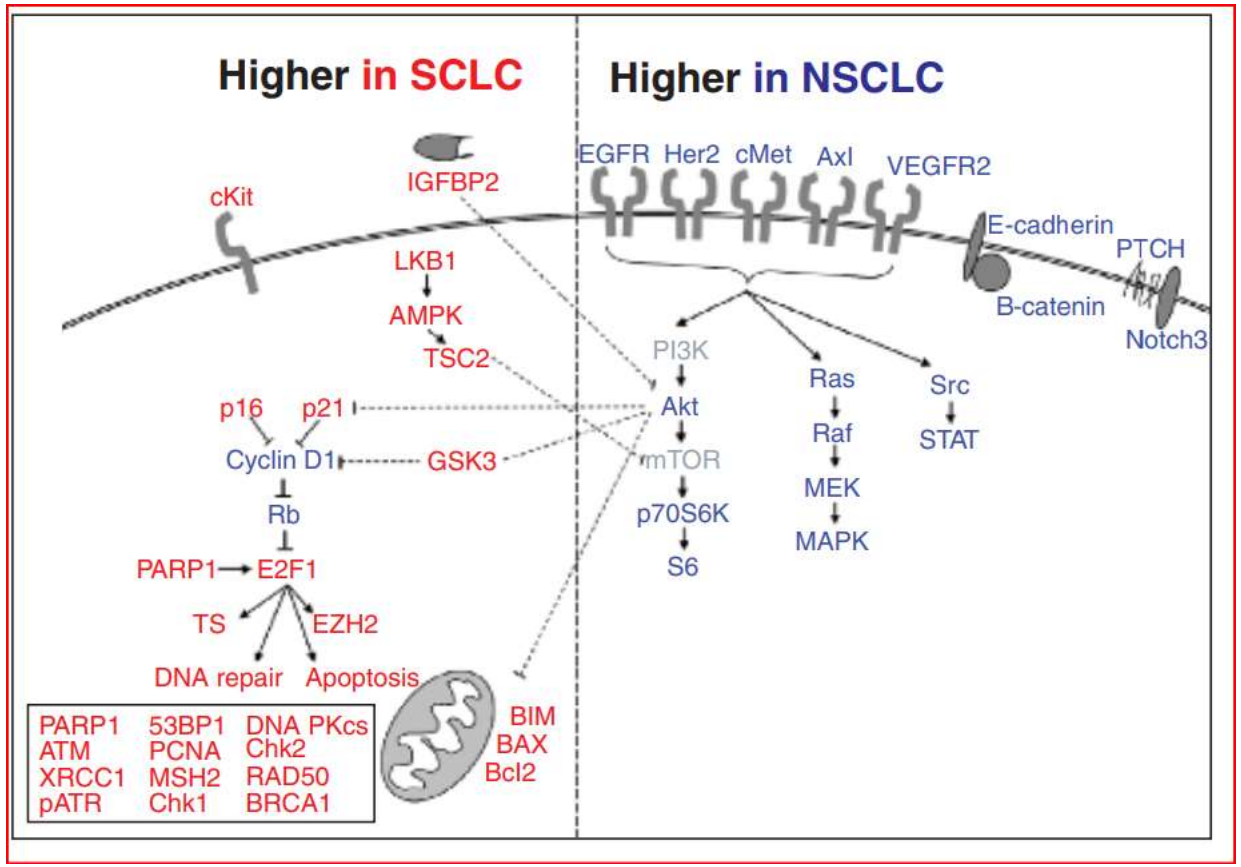
- Histology/IHC – showed SCLC is heterogenous
  - Small blue cells under microscope
  - Express neuroendocrine markers (chromogranin, synaptophysin, Insulinoma-associated protein 1 (INSM1))
  - Express specific markers ASCL1, NEUROD1, POU2F3

- Mutational analysis – showed multiple loss of gene mutations with high mutation burden
- Major genomic abberations
- Loss of TP53 and RB1
- LACK OF TARGETABLE RECURRENT GENOMIC ALTERATIONS



George J et al. Nature. 2015 Aug 6;524(7563):47-53

- Proteomics- showed SCLC express multiple down stream factors of transcription factors
- High expression of proteins involved in DNA damage
- Identification of major targets – PARP, ATR, PLK1, AURKA



Byers LA et al Cancer Discov. 2012 Sep;2(9):798-811

Targeting MYC			
MRT-2359	1/2	Any solid tumour with L-MYC or N-MYC expression, including SCLC	NCT05546268
Targeting SLFN11			
Olaparib and bevacizumab	1	SCLC with ATM deficiency, SLFN11-positive, or POU2F3-positive, established by immunohistochemistry and homologous recombination deficiency pathway gene mutations	NCT04939662
Targeting SEZ-6			
ABBV-706, cisplatin, carboplatin, and budigalimab	1/2	Multiple cohorts, including relapsed or refractory SCLC, glioblastoma, and NETs, with requirement for SEZ-6 expression in some cohorts	NCT05599984
EZH2 inhibitors			
Tazemetostat	1	Relapsed or recurrent SCLC after at least platinum doublet in patients with limited stage SCLC or chemo-immunotherapy in patients with extensive stage SCLC	NCT05353439
Mevrometostat	1	Relapsed or refractory SCLC, castration-resistant prostate cancer, and follicular lymphoma	PF-06821497

Immunotherapy in SCLC

- Pros
  - High mutational burden
  - Genomic instability

- Cons – IMMUNOSUPPRESSIVE PHENOTYPE
  - Low/absent T-lymphocytes
  - Low MHC class I expression
  - Low PD-L1 expression

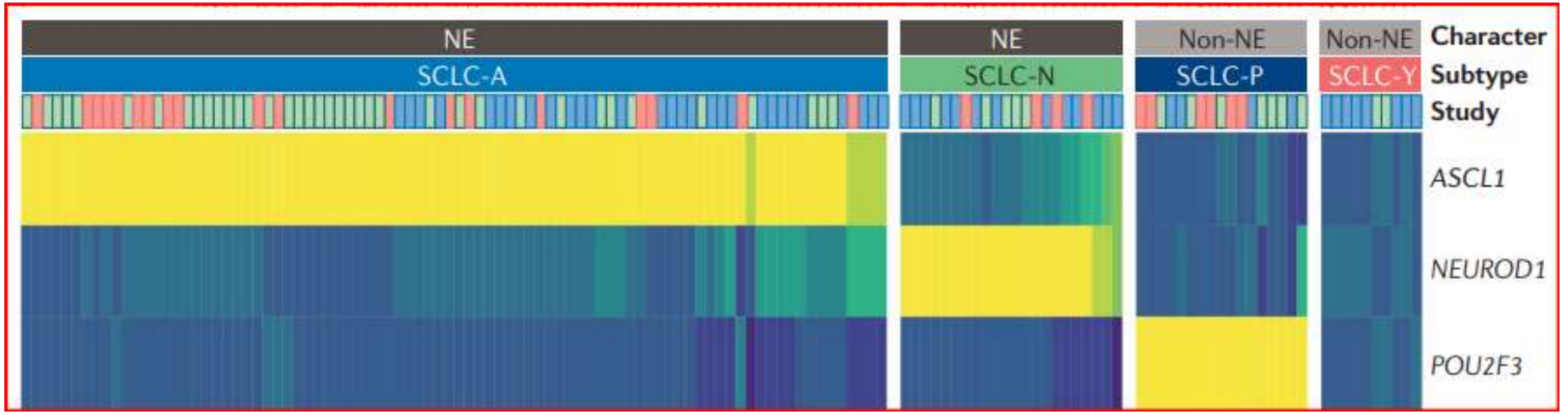
- In order to increase effect of immunotherapy – epigenetic modifiers can be used to cause increased expression of MHC

  Eg. LSD1 inhibitors

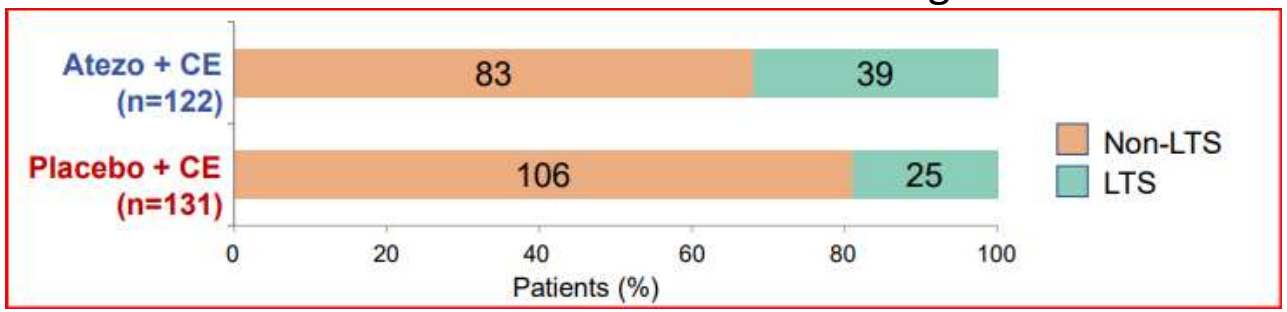
- Change cold tumor to hot i.e., low T cell to high T cell → use of DNA damage response – PARP inhibition (like talazoparib)

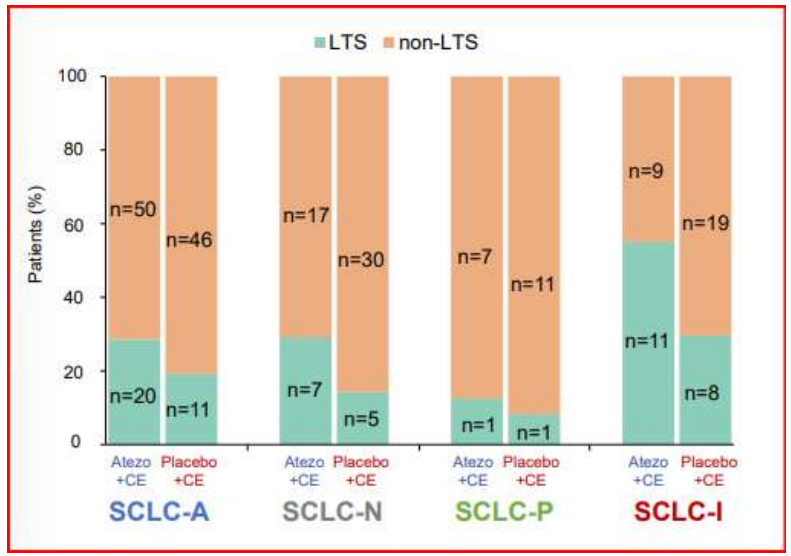
  CHK1, WEE1, ATR inhibitors

- DLL3 expression – used in DELLphi 301



- SCLC subtypes – ASCL1, NEUROD1, POUF2F3, inflamed
- Gay CM et conducted post hoc analysis from 271 of 403 patients recruited in IMpower133 – whose RNA-seq biomarker is available and classified them as long term survivor vs non LTS





Molecular classification and biomarkers of outcome with immunotherapy in extensive-stage small-cell lung cancer: analyses of the CASPIAN phase 3 study

Mingchao Xie[1], Miljenka Vuko[2], Jaime Rodriquez-Canales[3], Johannes Zimmermann[2], Markus Schick[2], Cathy O'Brien[4],

THANK YOU